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Review Article

Not breathing is not an option: How to deal with oxidative DNA damage

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ABSTRACT

Oxidative DNA damage constitutes a major threat to genetic integrity, and has thus been implicated in the pathogenesis of a wide variety of diseases, including cancer and neurodegeneration. 7,8-dihydro-8oxo-deoxyGuanine (8-oxo-G) is one of the best characterised oxidative DNA lesions, and it can give rise to point mutations due to its miscoding potential that instructs most DNA polymerases (Pols) to preferentially insert Adenine (A) opposite 8-oxo-G instead of the correct Cytosine (C). If uncorrected, A:8-oxo-G mispairs can give rise to C:G → A:T transversion mutations. Cells have evolved a variety of pathways to mitigate the mutational potential of 8-oxo-G that include i) mechanisms to avoid incorporation of oxidized nucleotides into DNA through nucleotide pool sanitisation enzymes (by MTH1, MTH2, MTH3 and NUDT5), ii) base excision repair (BER) of 8-oxo-G in DNA (involving MUTYH, OGG1, Pol λ, and other components of the BER machinery), and iii) faithful bypass of 8-oxo-G lesions during replication (using a switch between replicative Pols and Pol λ). In the following, the fate of 8-oxo-G in mammalian cells is reviewed in detail. The differential origins of 8-oxo-G in DNA and its consequences for genetic stability will be covered. This will be followed by a thorough discussion of the different mechanisms in place to cope with 8-oxo-G with an emphasis on Pol λ-mediated correct bypass of 8-oxo-G during MUTYH-initiated BER as well as replication across 8-oxo-G. Furthermore, the multitude of mechanisms in place to regulate key proteins involved in 8-oxo-G repair will be reviewed. Novel functions of 8-oxo-G as an epigenetic-like regulator and insights into the repair of 8-oxo-G within the cellular context will be touched upon. Finally, a discussion will outline the relevance of 8-oxo-G and the proteins involved in dealing with 8-oxo-G to human diseases with a special emphasis on cancer.

1. Introduction: oxidative stress and the chemical instability of DNA

As with the majority of things in life, there usually is a downside to even the most positive aspects. The validity of this almost universal principle holds even when it comes to one of the absolutely central ingredients of life for most prokaryotic cells and all eukaryotes, namely oxygen (O_2). While all aerobic life is absolutely dependent on O_2 to fuel basic chemical cellular reactions that produce energy and a vast variety of other essential metabolites, one of the most problematic aspects of O_2 consumption comes with its chemically reactive potential that gives rise to reactive oxygen species (ROS). ROS arise from a variety of sources, such as oxidative respiration in mitochondria, redox-cycling events involving Fenton reactions that are mediated by heavy metals, and as consequence of exposure to ionizing radiation, chemotherapy, transition metals, chemical oxidants and food (reviewed in [1]). Furthermore, ROS produced by macrophages, neutrophils and certain epithelial cells are essential agents to combat pathogens at the sites of infections, and also have a key role in inflammatory processes [2]. ROS species present in cells comprise agents such as superoxide anions ($\cdot O_2^-$), hydrogen peroxided (H_2O_2), and hydroxyl radicals ($\cdot$OH). Even though H_2O_2 is chemically less reactive than some other ROS, it has a high capacity for damage generation in a cell due to its ability to easily diffuse through biological membranes and thus reach other cellular compartments very quickly [3]. To counteract or neutralize the generation of ROS, cells are equipped with a variety of enzymatic and non-enzymatic antioxidants [4]. However, when the intracellular levels of ROS rise above the scavenging capacity of these antioxidants, cells come into a state of oxidative stress. The problem with such states of oxidative stress is, that ROS can inflict damage on many cellular macromolecules, such as proteins, lipids, RNA and DNA. Whereas lipids, proteins and also RNA can be turned over and replaced entirely rather easily by resynthesis, damaged DNA cannot [5,6]. In general, oxidative stress is widely attributed to promote chronic inflammation, genomic instability and human diseases [7].

Albeit being the central coding element that forms the basis of life (with the exception of RNA viruses), DNA is, chemically speaking, a remarkably unstable molecule [8]. Damage to DNA can be inflicted by exogenous physical and chemical agents (*e.g.* UV-irradiation, tobacco smoke, and DNA methylating agents). However, a detail that often falls

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into oblivion is that, due to its inherent instability, DNA undergoes a plethora of spontaneous alterations even under absolutely physiological circumstances and in the absence of any exogenous DNA damaging agents. This ubiquitous type of DNA damage, mostly referred to as endogenous DNA damage (as compared to the exogenous type), mostly originates from spontaneous hydrolytic reactions, as well as the aforementioned intracellular ROS [1]. Indeed, it has been estimated that as many as 20′000 DNA base lesions are generated every single day in every single cell under physiological, unstressed conditions through hydrolysis, oxidation, and non-enzymatic methylation alone [8]. These lesions, if left unrepaired, pose a serious threat to genetic integrity and can entail severe adverse consequences, such as cellular dysfunction, cell death or oncogenic transformation. Thus, genetic integrity is not only under threat during pathological states, such as oxidative stress, but is continuously challenged due to the inherent nature of its physiological environment.

2. 8-oxo-G

2.1. 8-oxo-G formation in DNA

While ROS can cause a wide variety of different DNA damages involving different DNA bases (reviewed in [1]), the base Guanine (G) is especially vulnerable to oxidation, due to its low redox potential [9]. This leads to the presence of several different oxidized G products in DNA, as well as the ribonucleotide pool, which will be discussed in Section 2.2. Among the different DNA lesions that are generated by ROS, one of the most abundant and certainly best characterised lesions is 7,8-dihydro-8-oxo-2′-deoxy-Guanine, or short “8-oxo-G” [9,10]. 8-oxo-G is generated through the introduction of an oxo group on the carbon 8 (C8) and the addition of a hydrogen atom to the nitrogen at position 7 (N7) of deoxy-Guanine (Fig. 1A and B). Estimates of 8-oxo-G lesions hover around 10^3 per cell per day under physiological circumstances in normal tissues, and values up to 10^5 lesions/cell have been reported in cancer cells [11,12]. Indeed, levels of 8-oxo-G are often used as biomarker to gauge the extent of oxidative stress of individual cells or organisms, and are even taken into account as a factor in risk assessment for many different diseases including cancer [13]. Due to certain methodological limitations and the relative propensity of G to be oxidized into 8-oxo-G even during extraction and quantification, not all of the data regarding 8-oxo-G levels can be taken at face value, but certainly the plethora of findings nicely underlines the biological significance of DNA damage caused by ROS.

When present in DNA, the main problem with 8-oxo-G arises during the cellular S-phase, in which the cell has to produce an accurate copy of the entire genome, so both daughter cells can inherit the identical encoded information. In contrast to many other DNA lesions, 8-oxo-G is not considered a blocking lesion that would stall the progression of the replication fork [14,15]. Instead, 8-oxo-G functionally mimics a Thymine (T) in *syn* conformation. This leads to stable formation of a pro-mutagenic A(*anti*):8-oxo-G(*syn*) mispair instead of the non-mutagenic C(*anti*):8-oxo-G(*anti*) base pair [9] (Fig. 1C and D). As a consequence of this stable A:8-oxo-G Hoogsteen base (mis-)pairing, replicative DNA polymerases (Pols) efficiently and frequently insert the incorrect A opposite 8-oxo-G instead of the correct C (*e.g.* [14,16–18] and many more). More problematically still, the A:8-oxo-G mispair evades proofreading, the inbuilt error-detection mechanism found in high-fidelity replicative Pols, because it mimics a cognate base pair and thus fails to cause significant helix-distortions in the DNA backbone [19]. Instead, the correct C:8-oxo-G Watson-Crick base pair is recognized as a mismatch, which consequently leads to a much lower efficiency of C incorporation opposite 8-oxo-G and explains the mutagenic properties of this lesion. If the A:8-oxo-G mispair goes uncorrected, one of the daughter cells will obtain a DNA template that harbours a point mutation at the site of 8-oxo-G, thus inheriting a C:G → A:T transversion mutation (Fig. 2A). Concluding, A inserted opposite 8-oxo-G acts similarly to a wolf in sheep’s clothing by pretending to be a correct base pair, while being a common source for point mutations in reality. The details of repair of 8-oxo-G will be discussed in Section 4.

2.2. 8-oxo-G formation in the nucleotide pool

As essential building blocks for life, desoxyribonucleotides (dNTPs), the precursors of DNA are not exempt from the threat emanating from ROS. Apart from attacking DNA bases directly, as discussed above, ROS also cause oxidation of the dNTP pool present in cells. As starting material to build DNA, oxidatively (or otherwise) damaged dNTPs pose a serious threat for genetic integrity when incorporated into nascent DNA either during DNA replication or repair. Indeed, dGTP seems to be even more susceptible to oxidation than G in DNA [20]. Thus, the problem of 8-oxo-G formation in DNA does not only arise from oxidation of a C:G base pair, but also from transactions that necessitate synthesis of new DNA where oxidatively damaged 8-oxo-dGTP can be incorporated opposite undamaged templating bases (Fig. 2B).

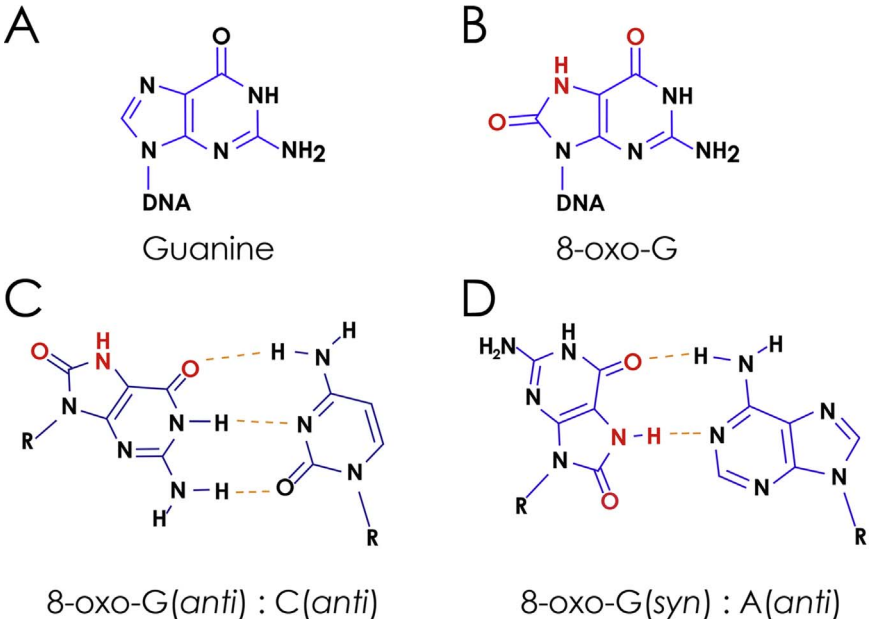

Fig. 1. Structures of 8-oxo-Guanine and its base-pairs. A) and B): Chemical structure of A) unaltered Guanine and B) 8-oxo-Guanine. The residues of 8-oxo-G that differ from normal G and are involved in base-pairing are coloured red. C) and D): Chemical structure of C) 8-oxo-G:C Watson-Crick and D) 8-oxo-G:A Hoogsteen base pairs. The hydrogen bonds contributing to base pairing are indicated by yellow dashed lines.

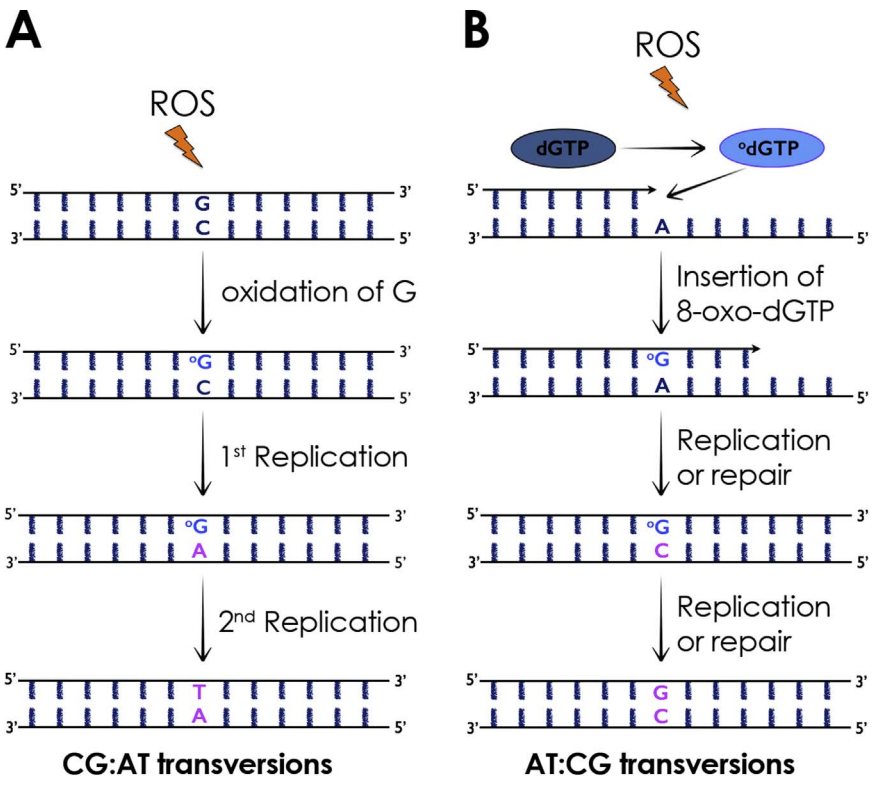

Fig. 2. Mechanism of 8-oxo-Guanine-induced mutations. 8-oxo-G can be introduced into DNA through 2 different mechanisms. A) Reactive oxygen species (ROS) can directly attack DNA, thus causing oxidation of G in the context of C:G which forms C:8-oxo-G base pairs. If replication across 8-oxo-G occurs, 8-oxo-G is often bypassed erroneously and A is inserted, giving rise to A:8-oxo-G base pairs. If left uncorrected, a 2nd round of replication will lead to fixation of a A:T base pair. Such a scenario leads to C:G → A:T transversion mutations. B) ROS can also cause oxidation of the nucleotide pool, thus giving rise to 8-oxo-dGTP (^{o}dGTP), which can be inserted opposite A to yield an A:8-oxo-G base pair. Replication or inappropriate MUTYH-initiated excision of A from A:8-oxo-G base pairs can cause C:8-oxo-G base pairs to form. C:8-oxo-G base pairs are substrate for OGG1-mediated repair, which removes the 8-oxo-G and replaces it with a G, giving rise to an A:T → C:G transversion mutation.

Currently there are 17 known human Pols that, as the name suggests, polymerise growing chains of DNA by incorporation of dNTPs opposite a DNA template [21,22]. Depending on its specific properties, each of these Pols will intrinsically incorporate damaged nucleotides with a different propensity. Determinants for incorporation of damaged nucleotides are features of the Pol itself, such as the structure of the active site and its relative 'flexibility' or 'rigidity' to accommodate and productively process unconventional base pairings, the structure of the nucleotide binding pocket, as well as the access of the respective Pol to the site of DNA synthesis. This last aspect is important to remember, as, regardless how promiscuous a certain Pol might be, if it does not gain access to actually perform DNA synthesis, it will not be able to do harm. From this, one can directly infer the importance of a very tight regulation especially of the more promiscuous Pols, as will be discussed in detail in Section 5. Though nature has devised mechanisms to reduce the burden of 8-oxo-dGTP in the nucleotide pool (see Section 4.3), nevertheless the incorporation of oxidatively damaged dNTPs poses a real threat to genetic integrity [23,24].

Incorporation of 8-oxo-dGTP has been shown to be catalysed by many different Pols across all families and reverse transcriptases into DNA and RNA, and the incorporation efficiencies as well as preference for either a templating A or C depend on the individual Pol and whether 8-oxo-dGTP adapts a *syn* or *anti* conformation during base pairing (*e.g.* [24–37] and Table 1). Incorporation of 8-oxo-dGTP by Pols has been shown to generate A:T → C:G mutations (Fig. 2B) [38–41]. The preferences of different Pols to incorporate 8-oxo-dGTP opposite templating A or C are summarized in Table 1.

As has been discussed above in Section 2.1, a Watson-Crick C:8-oxo-G pairing causes template and polymerase distortions and thus rather poses problems than the Hoogsteen base pairing adapted by A:8-oxo-G [19], which is consistent with Pols in general preferentially inserting 8-oxo-dGTP opposite templating A (Table 1 and references therein). Of note, this lower preference for insertion of 8-oxo-dGTP opposite C caused problems to crystallize a complex of 8-oxo-dGTP paired to C for a long time, while crystals of A:8-oxo-dGTP were achievable. Structural studies suggest that while the flexibility around the template-binding pocket of a Pol can permit 8-oxo-G to base pair both in Watson-Crick as well as Hoogsteen base pairing, the binding pocket for incoming nucleotides does not have such flexibility and thus strongly discourages insertion of 8-oxo-dGTP opposite C, as demonstrated for Pol β [55]. Finally, insertion of 8-oxo-dGTP opposite either templating base by Pol β has been shown to lead to a cytotoxic nicked repair intermediate due to loss of hydrogen-bonding interactions between the bases that causes DNA synthesis to pause [45]. In contrast, another study found that ligation after 8-oxo-dGTP insertion by Pol β into a single nucleotide gap by DNA ligase I was productive in the context of both templating bases, though possibly a bit less efficient when 8-oxo-dGTP was inserted opposite C [43]. Overall, it seems that the proofreading activity of 8-oxo-dGTP inserted opposite A depends highly on the Pol in question, and possibly also the experimental reaction conditions used to probe this question.

The problem succeeding insertion of 8-oxo-dGTP into nascent DNA is outlined in the following: if 8-oxo-dGTP is inserted opposite C, removal of 8-oxo-G from C:8-oxo-G base pairs is relatively unproblematic through activity of the 8-oxo-G specific DNA glycosylase OGG1, as discussed in detail in Section 4.1. If however 8-oxo-dGTP is inserted opposite A (Fig. 2B), repair of the resulting A:8-oxo-G base pair faces a conundrum: A:8-oxo-G base pairs are the substrate for DNA glycosylase MUTYH, which excises the A from A:8-oxo-G base pairs [56]. Yet, such MUTYH-catalysed excision of A and subsequent replacement with C (as discussed in detail in Section 4.1) would result in fixation of the wrong C:8-oxo-G base pair in this particular situation. Thus, 8-oxo-dGTP insertion into DNA has the potential to lead to A:T → C:G transversion mutations. Indeed, 8-oxo-dGTP has been shown to cause such A:T → C:G transversions in mammalian cells [57,58]. To circumvent such mutations, it is assumed that cells would opt to avoid activity of MUTYH in these situations. Instead, to resolve this state of affairs, mismatch repair potentially steps in at this point, as discussed later in Sections 4.2 and 8.3.

In light of the obvious preference of many Pols to insert 8-oxo-G opposite the incorrect A, it comes as somewhat of a relief to know that the efficiency to incorporate 8-oxo-dGTP instead of the normal dNTPs is

Table 1
Templating base preference for incorporation of 8-oxo-dGTP by various Pols.

Favoured template	DNA Polymerase	DNA Pol Family	Template preference dA/dC	Refs.
dA > > > dC	hPolι	Y	dA only	[30]
	hPolη	Y	> 180:1, 660:1	[30,37]
	Dbh *(Sulfolobus solfataricus)*	Y	dA only	[42]
	Dpo4 *(Sulfolobus solfataricus)*	Y	dA only	[42]
dA > dC	hPolβ	X	10.5:1, 24:1, 40:1	[43–45]
	hPolλ	X	34.5:1, 4.5:1	[36,43]
	hPolγ	A	13:1, 66.7:1	[46,47]
	hPolκ	Y	11:1	[37]
	T7exo$^-$ *(T7 bacteriophage)*	A	31:1	[26]
	Pol III *(Escherichia coli)*	C	20:1	[41]
	Pol IV *(Escherichia coli)*	Y	N.d.	[48]
	Pol I BF *(Bacillus stearothermophilus)*	A	12.7:1	[33]
	Pol X *(Thermus thermophilus)*	X	43.3:1	[34]
	DinB2 *(Mycobacterium smegmatis)*	Y	N.d.	[49]
dA ≅ dC	Pol4 *(Schizosaccharomyces pombe)*	X	1.08:1	[35]
	KFexo$^-$ *(Escherichia coli)*	A	1.6:1, 0.44:1	[26,50]
	α subunit Pol III *(Escherichia coli)*	C	1.3:1	[51]
	HIV-1 RT *(Human Immunodeficiency virus)*	RT	0.5:1	[26]
	ASFV Pol X *(African swine fever virus)*	X	0.5:1	[29]
	φ29 Pol *(Bacillus subtilis phage φ29)*	B	0.33:1	[52]
	DNA Pol B1 *(Sulfolobus solfataricus)*	B	N.d.	[42]
dA < dC	hPolα	B	0.146:1	[33]
	Bovine Polδ + PCNA	B	0.032:1	[53]
	Pol II exo$^-$ *(Escherichia coli)*	B	0.045:1	[26]

Table modified *after* [54]. The ratio dA/dC is the ratio of efficiency of 8-oxo-dGTP incorporation opposite templating dA or dC, as determined from k_{cat}/k_m, v_{max}/k_m or k_{pol}/k_d. 'h' before Pol stands for human. N.d. = ratio could not be determined. RT = reverse transcriptase.

Table 2
Relative efficiencies of various DNA Polymerases for incorporating 8-oxo-dGTP compared to incorporation of normal dNTPs.

DNA Polymerase	DNA Pol Family	Efficiency of 8-oxo-dGTP incorporation	Refs.
hPolγ	A	1×10^{-4}	[46]
KFexo$^-$ *(Escherichia coli)*	A	1.2×10^{-2}	[26]
		7.2×10^{-4}	[50]
		6.4×10^{-6}	[59]
T7exo$^-$ *(T7 bacteriophage)*	A	9.1×10^{-6}	[26]
Pol I BF *(Bacillus stearothermophilus)*	A	1.07	[33]
hPolα	B	7.3×10^{-4}	[33]
Bovine Polα	B	1.5×10^{-2}	[59]
Bovine Polδ + PCNA	B	$\sim 10^{-3}$	[53]
φ29 Pol *(Bacillus subtilis phage φ29)*	B	5.0×10^{-4}	[52]
Pol II exo$^-$ *(Escherichia coli)*	B	3.1×10^{-6}	[26]
Pol III *(Escherichia coli)*	C	5.6×10^{-2}	[41]
α subunit Pol III *(Escherichia coli)*	C	3.9×10^{-2}	[51]
hPolβ	X	1.8×10^{-1}	[43]
		8.0×10^{-3}	[44]
hPolλ	X	4.7×10^{-3}	[36]
		7.5×10^{-2}	[43]
Pol X *(Thermus thermophilus)*	X	6.5×10^{-2}	[34]
Pol4 *(Schizosaccharomyces pombe)*	X	4.04×10^{-2}	[35]
ASFV Pol X *(African swine fever virus)*	X	1.3×10^{-3}	[29]
hPolι	Y	1.7×10^{-2}	[30]
hPolη	Y	1.5×10^{-1}	[30]
		5.9×10^{-1}	[37]
hPolκ	Y	7.9×10^{-3}	[37]

Table modified after [54]. The efficiency of 8-oxo-dGTP incorporation opposite the favourite templating base compared to incorporation of normal dNTPs opposite that same base, as determined from k_{cat}/k_m, v_{max}/k_m or k_{pol}/k_d. 'h' before Pol stands for human.

rather low, especially for the replicative DNA Pols of the B-family that have been tested so far (Table 2). Nevertheless, the danger of incorporating 8-oxo-dGTP during transactions carried out by Pols should not be underestimated.

Some of the open questions in the field are which of the Pols leads to incorporation of 8-oxo-dGTP into DNA *in vivo*, under which circumstances this happens, and whether insertion of an 8-oxo-dGTP by replicative Pols triggers proofreading activity or even initiates a Pol switch to continuously promote DNA synthesis. Furthermore, it would be interesting to get an understanding for the exact amounts of oxidized nucleotides present in cells under specific circumstances.

Among the possible culprits, for obvious reasons, the more promiscuous repair Pols have been investigated for their contribution to 8-oxo-dGTP insertion. Pol β, Pol η, REV1, Pol ζ, Pol κ have all been implicated to have their share in catalysing 8-oxo-dGTP incorporation into DNA *in vivo*. Nevertheless, also the replicative Pols − by nature much less prone to catalyse incorrect insertion of nucleotides − might contribute to this phenomenon (reviewed in [60]). It thus remains to be addressed how exactly cells deal with such situations to alleviate both the mutational as well as the potentially cytotoxic potential that results from 8-oxo-dGTP insertion.

3. DNA base excision repair

To counteract the possibly deleterious effects that DNA damage and mutations can have, cells have evolved an intricate network of DNA repair pathways that constantly sense, report and correct aberrations in DNA caused by all kinds of endogenous and exogenous DNA damage [61]. The major cellular repair pathway responsible for repair of the majority of DNA lesions deriving from endogenous sources, such as ROS, is base excision repair (BER). The task of BER is to repair the multitude of frequent, constantly arising DNA base alterations and single-strand breaks (SSBs), prompting a comparison with the role of a cellular housekeeper engaged to keep genomic DNA tidy and clean [62]. Interestingly, it seems that cells have difficulties living without their housekeeper: knocking out any of the core BER pathway genes (APE1, XRCC1, Pol β, or DNA ligase III) is embryonically lethal (see also Table 3 and the relevant text sections) [62]. This has been widely attributed as clear evidence for the importance of not having too much DNA damage in cells in order to survive. It might however also be at least partly caused by the fact, that the core BER machinery is critically involved in active DNA demethylation, a crucial mechanism involved in embryonic development [63].

Depending on the nature of the lesion that needs to be taken care of,

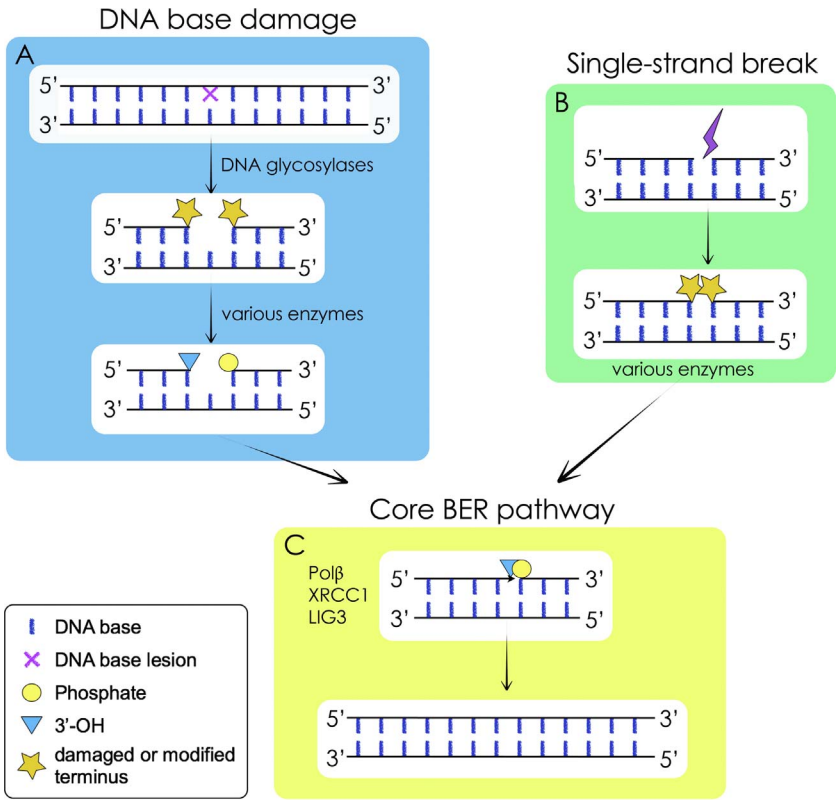

Fig. 3. Simplified schematic overview of Base Excision Repair. Modified from [198]. (A) BER is initiated by damage-specific DNA glycosylases, which identify and release the corrupted base by hydrolysis of the N-glycosylic bond linking the DNA base to the sugar phosphate backbone (reviewed in [229]). The arising abasic (AP) site is further processed by AP-endonuclease 1 (APE1), and depending on the mechanism by which the DNA base was removed, end processing of the modified 3′- and 5′-termini is performed by a variety of end-processing enzymes. This processing results in the generation of a 3′-OH and a 5′-P group adjacent to the DNA gap or break. (B) Single-strand breaks (SSBs) can also arise from direct disintegration of oxidized deoxyribose. This process usually leads to damaged or modified termini, which are processed by a variety of enzymes to 3′-OH and 5′-P groups. SSBs are then handled identically to the BER intermediates from this point onward. (C) Further processing of the SSB containing intermediate stemming from either source is carried out by the core BER complex. Shown here is the short-patch BER subpathway that includes DNA polymerase β (Pol β), XRCC1 (X-ray repair cross-complementation group 1) and DNA ligase IIIa (Lig III). Pol β possesses a dRP-lyase activity that removes the 5′-sugar phosphate and also, functioning as a DNA polymerase, adds one nucleotide to the 3′-end of the arising single-nucleotide gap. Finally, the XRCC1-Lig III complex seals the DNA ends, therefore accomplishing complete DNA repair [62].

BER can proceed *via* two different repair subpathways, short-patch (replacing only the damaged nucleotide) or long-patch BER (which replaces a stretch of 2–12 nucleotides starting at the damaged site) (Fig. 3) [62]. The classical short-patch BER pathway is initiated by one of the many different DNA glycosylases present in cells, each of which recognizes a subset of different damaged bases [64]. Depending on the identity of the glycosylase, it only catalyses the release of the corrupted base by hydrolysis of the N-glycosylic bond that links the DNA base to its sugar backbone, thus creating an abasic site (AP-site), or promotes further incision of the phosphodiester backbone to yield a 1 nucleotide gap with modified DNA termini. The resulting intermediates are further processed by AP-endonuclease 1 (APE1), Polynucleotide phosphatase/kinase (PNKP), or other 'end processing enzymes' which tailor the DNA ends to be compatible with DNA synthesis and ligation. At this point, classical BER converges with repair of SSBs, which are another type of lesion very frequently formed by ROS [65]. As the name suggests, SSBs are discontinuities in one strand of the DNA double helix, usually accompanied by loss of a single nucleotide and often harbouring chemically modified DNA termini surrounding the break. Once the 3′ terminus has been "cleaned up" to be an OH group (prerequisite for Pols to insert a nucleotide), the so-called core BER complex consisting of Pol β (Pol β), X-ray repair cross-complementing protein 1 (XRCC1), and DNA ligase IIIa (Lig IIIa) steps into action. Pol β utilizes its dRP-lyase activity to remove the downstream 5′sugar phosphate and inserts one nucleotide into the gap, whereupon Lig IIIa catalyses ligation of the 3′OH group of the newly inserted nucleotide with the downstream 5′P, thus completing the short-patch BER subpathway. If the 5′-ends are blocked and cannot be processed by the available end-processing enzymes, BER can proceed *via* a long-patch sub-pathway, that leads to a replacement of 2–12 nucleotides and utilizes a switch from Pol β to the replicative Pol δ [62]. In this scenario, the displaced DNA flap of 2–12 nucleotides is cut off by flap endonuclease 1 (FEN1) and ligation occurs through DNA ligase I.

4. Dealing with 8-oxo-G

As discussed in Section 2, ROS can lead to direct formation of 8-oxo-G in DNA, as well as give rise to the oxidation product 8-oxo-dGTP nucleotide pool. To keep the mutational burden stemming from these two sources of oxidized G in check, organisms employ various enzyme systems designed to counteract this oxidative threat. Mechanisms to subdue the mutational burden of these oxidized G products involve repair of 8-oxo-G that can be found in DNA, removal of oxidized nucleotides from the ribonucleotide pool to avoid their incorporation into nascent DNA, as well as ways for the replication fork to correctly bypass 8-oxo-G lesions encountered during replication (Fig. 4). The variety of contexts that 8-oxo-G can be found in reflects directly in the variety of mechanisms that have been described to be utilized for repair, removal or bypass of 8-oxo-G damage. In the following, the different mechanisms utilized by the cell to lower the impact of 8-oxo-G in these diverse contexts will be discussed.

4.1. Base excision repair of 8-oxo-G in DNA

The bulk of 8-oxo-G lesions in genomic DNA are dealt with by BER, and this involves a multistep process as well as the involvement of different key players depending on whether A:8-oxo-G or C:8-oxo-G base pairs are the substrate to be addressed (Fig. 5). Additional mechanisms that contribute to repair of 8-oxo-G in DNA are discussed in Section 4.2.

In principle, C:8-oxo-G base pairs can be formed whenever oxidative stress impinges on double-stranded DNA and leads to oxidation of G in the context of a C:G base pair. The fate of this newly formed C:8-oxo-G base pair is now much dependent on the cell cycle: if this particular stretch of DNA is not currently undergoing replication, the DNA glycosylase OGG1 is capable of recognizing C:8-oxo-G base pairs and subsequently remove 8-oxo-G. The resulting 1 nucleotide gap is then processed by APE1 and the canonical BER core complex Pol β – XRCC1 – Lig IIIa restores a fully double-stranded piece of DNA containing a

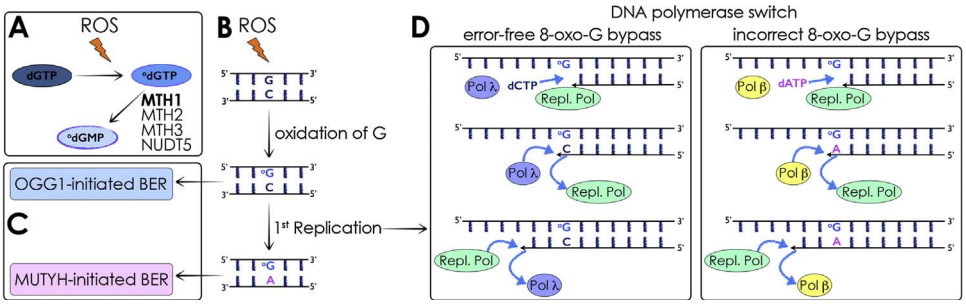

Fig. 4. The various ways to deal with 8-oxo-G. Cells employ 3 major pathways to deal with 8-oxo-G: nucleotide pool sanitisation, base excision repair (BER) of 8-oxo-G in DNA, and bypass of 8-oxo-G during replication by a DNA polymerase switch. (A) dGTP in the nucleotide pool is prone to oxidation by reactive oxygen species (ROS), giving rise to 8-oxo-dGTP (°dGTP). The four enzymes MTH1, MTH2, MTH3 and NUDT5 catalyse hydrolysis of 8-oxo-dGTP to produce the monophosphate compound 8-oxo-dGMP (°dGMP) and thus remove 8-oxo-dGTP from the nucleotide pool. MTH1 is highlighted in bold, because current evidence suggests that it has by far the most important role in sanitisation of 8-oxo-dGTP in mammalian cells. (B) ROS also attack DNA, causing oxidation of C:G which forms C:8-oxo-G base pairs. If replication across 8-oxo-G occurs, 8-oxo-G is often bypassed erroneously and A is inserted, giving rise to A:8-oxo-G base pairs. (C) C:8-oxo-G base pairs are substrate for OGG1-initiated BER, while A:8-oxo-G mispairs are processed through MUTYH-initiated BER. These two BER processes are discussed more in detail in Fig. 5. (D) Replication across 8-oxo-G can have two outcomes: insertion of correct C or incorrect A opposite 8-oxo-G. (left) Error-free bypass of 8-oxo-G by a replicative polymerase (Repl. Pol) is promoted by exchanging the Repl. Pol with Pol λ after insertion of correct dCTP. Pol λ is capable of preferentially extending C:8-oxo-G base pairs for a few nucleotides, after which Pol λ is replaced again by the Repl. Pol. (right) Incorrect bypass of 8-oxo-G instead is promoted by exchanging the Repl. Pol with Pols β or η after insertion of incorrect dATP. Pols β and η preferentially extend the wrong A:8-oxo-G base pairs for a few nucleotides, after which a switch back to the Repl. Pol occurs. For simplicity, only Pol β is indicated in the image, but Pol η has been shown to have the same effect.

correctly repaired G:C base pair (reviewed in [1]). If however the C:8-oxo-G base pair escapes repair and is utilized uncorrected as a template for DNA synthesis, replicative Pols frequently insert a wrong A opposite 8-oxo-G instead of the correct C, as discussed in Section 2. This gives rise to an A:8-oxo-G mispair. Importantly, the nucleotide that needs to be removed now is the undamaged A, and not the 8-oxo-G, because another round of replication would lead to fixation of the mutation in the form of a TA base pair, having caused a C:G → A:T transversion mutation. To remove the erroneously incorporated A from an A:8-oxo-G base pair, cells utilize the DNA glycosylase MUTYH [56]. MUTYH is a slightly unconventional glycosylase in that it does not remove a damaged nucleotide from DNA, but rather the undamaged A from opposite a damaged 8-oxo-G. This very important enzyme gives the cells 'a second chance' to correct what was wrongly inserted opposite 8-oxo-G

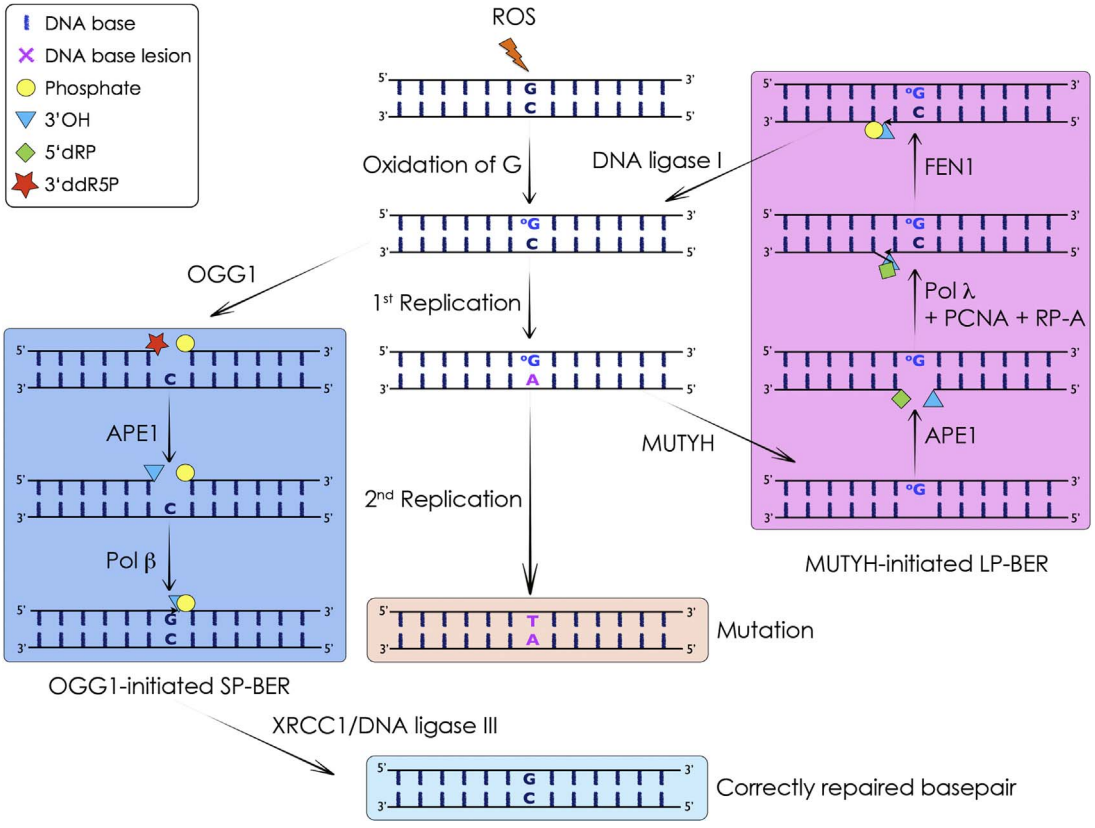

Fig. 5. MUTYH-initiated BER of A:8-oxo-G lesions. Modified from [56]. When ROS attack DNA, this leads to the formation of C:8-oxo-G base pairs through oxidation of G. (left column) These can be recognized by OGG1, which excises the 8-oxo-G and incises the resulting AP-site by β-elimination, giving rise to a 3′ddR5P and a 5′P residue. This 3′ sugar phosphate is then removed by APE1, yielding a 1 nucleotide gap with a 3′OH and a 5′P. Subsequently, pol β catalyses the insertion of a G opposite the templating C in this SP-BER pathway, and ligation by XRCC1/DNA ligase III leads to restoration of an intact, correctly base-paired double-stranded DNA again. (middle column) If the C:8-oxo-G base pairs are not recognized before S-phase by OGG1, or they arise through oxidation in S-phase, the replicative pols will often incorporate a wrong A opposite 8-oxo-G, giving rise to A:8-oxo-G mispairs. If these are not corrected, another round of replication will lead to a C:G- > A:T transversion mutation. (right column) The A:8-oxo-G base pairs can be recognized by MUTYH, which catalyses the excision of the wrong A from opposite 8-oxo-G, leading to the formation of an AP site. This AP site is further processed by APE1, which results in a 1 nt gap with 3′OH and 5′dRP moieties. The incorporation of the correct C opposite 8-oxo-G and one more nucleotide is performed by pol λ in collaboration with the cofactors PCNA and RP-A, thus performing strand displacement of the downstream DNA strand. FEN1 cleaves the 5′ flap, leading to a 5′P moiety, which can be ligated by DNA ligase I to yield an intact C:8-oxo-G containing double-stranded DNA. This C:8-oxo-G is then again substrate for OGG1-mediated removal of 8-oxo-G (left column).

in the first place. By doing so, MUTYH paves the way for a long-patch BER subpathway [16,66,67]. As in canonical BER, removal of the base by MUTYH is followed by tailoring of the DNA ends by APE1, so that a Pol can insert the correct C opposite 8-oxo-G. Nevertheless, as discussed already in Section 2, insertion of C opposite 8-oxo-G is something most Pols find difficult to do. Thus it was unclear for a long time, which Pol is responsible for inserting the correct nucleotide, as most examined pols showed significant error-prone bypass of 8-oxo-G. Over the last decade, accumulating evidence has clearly shown that Pol λ, a close relative of Pol β, is the one Pol to efficiently insert a correct C opposite 8-oxo-G when helped by the two cofactors Proliferating Cell Nuclear Antigen (PCNA) and Replication Protein A (RP-A) [16]. In fact, Pol λ together with PCNA and RP-A inserted 1200-fold more correct C opposite 8-oxo-G than incorrect A. Later on, this unique ability of Pol λ to catalyse C:8-oxo-G base pairs was found to result from a very flexible active site, capable of accommodating 8-oxo-G in both the *anti* and *syn* conformations, and from a kinetic switch that selectively discriminates against the pro-mutagenic *syn* conformation, thus shunting repair toward the correct C:8-oxo-G base pairing [68]. Interestingly, the auxiliary proteins PCNA and RP-A were found to act as molecular switches in this context to activate the error-free Pol λ-dependent 8-oxo-G bypass while at the same time repressing error-prone bypass by the canonical BER enzyme Pol β [66]. This Pol λ-mediated error-free repair of A:8-oxo-G mismatches was shown to utilize a long-patch BER mechanism by additionally replacing 1 nucleotide downstream from the original lesion, and thus require FEN1 as well as DNA ligase I to come to successful completion [67]. The resulting product of this error-free MUTYH and Pol λ-mediated repair pathway of A:8-oxo-G mismatches is an C:8-oxo-G base pair, which in turn is amenable to the OGG1-initiated short-patch BER reaction, as discussed above.

4.2. Additional mechanisms contributing to repair of 8-oxo-G in DNA

While repair of 8-oxo-G lesions in DNA is dominated by OGG1- and MUTYH- initiated BER, other DNA repair pathways have been found to contribute to keep the mutational burden of 8-oxo-G as low as possible. The list of involved players includes mismatch repair (MMR), transcription-coupled nucleotide excision repair (TC-NER), global-genome nucleotide excision repair (GG-NER), as well as a variety of other DNA glycosylases, as has been reviewed in detail in [1,69,70].

Mounting evidence suggests that the involvement of MMR in keeping 8-oxo-G levels in DNA under control is potentially *via* removing 8-oxo-G from 8-oxo-G:A mismatches that have arisen due to insertion of 8-oxo-dGTP. As already mentioned, the problem with insertion of 8-oxo-dGTP into nascent DNA is the following: if inserted opposite C, removal of 8-oxo-G from C:8-oxo-G base pairs should be relatively straight forward through activity of the 8-oxo-G specific DNA glycosylase OGG1, as discussed in the previous chapter. If however inserted opposite A (Fig. 2B), MUTYH-initiated repair of the resulting A:8-oxo-G base pair faces a problem: excision of A from A:8-oxo-G base pairs and subsequent replacement with C would result in fixation of the wrong 8-oxo-G:C base pair in this particular situation and lead to an A:T → C:G transversion mutation. To avoid this, it is assumed that cells would opt to avoid activity of MUTYH in these situations. Instead, to resolve this state of affairs, mismatch repair has shown to contribute to removal of 8-oxo-G that has arisen from insertion of 8-oxo-dGTP [23,59,71]. As MMR is closely linked to replication and one of its main functions is the correction of replication-caused mistakes by targeting its removal activity to the nascent strand, utilising MMR in this case seems an elegant solution to the problem. This would also explain the apparent synergistic action of MUTYH-initiated BER and MMR that has been often seen *in vivo*, as discussed later in Section 8.3. Details on this interaction between MUTYH and the MMR pathway have been reviewed recently in [60]. How the coordination between these different pathways is achieved to ensure proper processing of these lesions in the context of DNA replication still remains far from being understood.

4.3. Removal of 8-oxo-dGTP from the nucleotide pool

Removal of 8-oxo-dGTP from the nucleotide pools before it gets incorporated into DNA by Pols is an important pathway for safekeeping the genome from 8-oxo-G damage. To date there are 4 enzymes that have been described to catalyse the hydrolysis of a variety of different oxidised nucleotides including 8-oxo-dGTP: MutT homologue 1 (MTH1, sometimes referred to as NUDT1), MutT homologue 2 (MTH2, also known as NUDT15), MutT homologue 3 (MTH3 or NUDT18) and Nudix-type 5 (NUDT5) (Fig. 4A). These enzymes can catalyse the hydrolysis of 8-oxo-dGTP to 8-oxo-dGDP or 8-oxo-dGMP. As 8-oxo-dGMP cannot be used by Pols for DNA synthesis, this hydrolysis prevents incorporation of 8-oxo-dGTP into nascent DNA. The final degradation product, 8-oxo-dGMP, can not be reutilized either to produce 8-oxo-dGTP *via* phosphorylation through guanylate kinase, as this enzyme is not active on 8-oxo-dGMP (reviewed in [72]). Overall, current evidence suggests that MTH1 is the most important contributor to nucleotide pool sanitisation of 8-oxo-dGTP in mammalian cells, and the other three enzymes might play a backup-role for this nucleotide, while being relevant in the processing of other substrates. For an in-depth discussion of these enzymes the interested reader is referred to a recent review on pathways that control dNTP pools [60]. In summary, removal of 8-oxo-dGTP from the nucleotide pool is an important mechanism to mitigate the mutational potential of oxidised nucleotides that can otherwise be erroneously incorporated by Pols into DNA.

4.4. Bypass of 8-oxo-G during replication

Error-free replication of DNA is a very basic prerequisite of life for cells to divide and entire organisms to stay healthy. In an ideal world, all C:8-oxo-G base pairs would be repaired before the onset of replication. As however oxidation of G can occur throughout the entire cell cycle, DNA in S-phase is by no means exempt from the threat of ROS-induced DNA damage, such as 8-oxo-G. Thus, a scenario that has to be dealt with by the cell is the bypass of 8-oxo-G lesions during DNA replication.

As already discussed above, in contrast to many other DNA lesions, such as for instance UV-induced lesions that present a block to replicative Pols (reviewed *e.g.* in [73]), 8-oxo-G is not considered a blocking lesion *per se* [14,15,74]. Nevertheless, transient inhibition of DNA synthesis by different Pols (such as the Klenow fragment of *Escherichia coli* Pol I and calf thymus Pols α and δ) occurring 3′ to the templating 8-oxo-G has been documented, indicating that these Pols do slightly struggle with the lesion all the same [14,53]. Similarly, pol δ from human cells has been shown to transiently stall at sites of 8-oxo-G lesions [75]. Therefore, 8-oxo-G is not a stalling lesion, but still induces the replicative Pols to slow down during bypass. Furthermore, the *E.coli* Pol I Klenow fragment as well as calf thymus Pols α and δ were found to struggle with extension of correct C:8-oxo-G base pair and much more efficiently extended A:8-oxo-G mispairs [14,53]. Despite these dire prospects when replicative Pols encounter an 8-oxo-G, the overall *in vivo* mutation frequency of 8-oxo-G lesions in templating DNA without post-replication repair mechanisms has been estimated at around 19%, which is much lower than expected considering the replication bypass problems [74]. Therefore, a very central question emerges: how is correct bypass of 8-oxo-G by the replication machinery accomplished, when insertion of correct C opposite 8-oxo-G by replicative Pols is so hard to achieve and the extension of correct C:8-oxo-G base pairs so difficult? Addressing this exact question, it was found that human Pol δ pauses in front of 8-oxo-G, and then readily incorporates both C or A opposite the lesion [76]. When it came to extending past the lesion, however, the A:8-oxo-G mispairs were easily extended by Pol δ, in stark contrast to C:8-oxo-G base pairs, which led to stalling of Pol δ. It was further shown that the stalling of Pol δ after incorporation of correct C opposite 8-oxo-G could be overcome by Pol λ, Pol β, and Pol η, all of which assisted Pol δ to overcome the lesion. Most importantly,

however, these results demonstrated that only Pol λ was able to assist Pol δ to selectively perform the *correct* insertion of C opposite 8-oxo-G by specifically enhancing exclusively the correct bypass of 8-oxo-G using C, while Pols β and η lacked selectivity and even preferentially enhanced erroneous bypass of 8-oxo-G. These data suggested the existence of a DNA polymerase-switch between the replicative Pol δ and the repair Pol λ to promote error-free bypass of 8-oxo-G lesions in an efficient and accurate manner to counteract the mutational potential of 8-oxo-G (Fig. 4D). Indeed, Pol λ had been shown to preferentially extend C:8-oxo-G base pairs, with an efficiency even higher than that displayed on undamaged C:G base pairs [77]. Pol λ's unique proficiency to insert correct C opposite 8-oxo-G and preferentially extend C:8-oxo-G base pairs was shown to be courtesy of Pol λ's unique flexible active site and a specific kinetic switch that discriminates against pro-mutagenic bypass [68]. Interestingly, corroborating a possible role of Pol λ either directly at or shortly following the replication fork, silencing of Pol λ, but not Pol β, was found to cause replication stress and to activate the S-phase checkpoint [78]. Indeed, an impairment of the S-phase checkpoint was synthetically lethal when combined with silencing of Pol λ in cancer cells. More recently, the existence of a DNA polymerase-switch between a replicative Pol and Pol λ that promotes error-free bypass of 8-oxo-G lesions has been independently confirmed [79]. Significantly, as had been observed initially [76], this study also reported an increase in small deletions at the site of 8-oxo-G when Pol λ was absent from the cells. These findings are in line with a role of Pol λ in extending the C:8-oxo-G base pair for a few nucleotides, which, as discussed above is a feature replicative Pols struggle with. Once the C:8-oxo-G base pair has been extended by Pol λ sufficiently, the replicative Pols take over again to continue replication as usual. Searching for factors responsible of influencing this DNA polymerase-switch between Pol δ and Pol λ at 8-oxo-G lesions, it was found that Pol δ interacting protein 2 (PolDIP2) could physically interact with Pol λ and thus increase both the processivity as well as the catalytic efficiency of the error-free bypass of 8-oxo-G by Pol λ as well as Pol η [80].

Among the many questions that remain open are: how exactly is the switch between Pol δ and Pol λ coordinated during replication? Do PCNA and RP-A have a modulatory role in this? While mono-ubiquitination of PCNA was not found to influence the switch reaction [76], how does the replication fork signal the need to switch Pols at 8-oxo-G? These and many other details regarding the synthesis past 8-oxo-G will hopefully be clarified in the future.

4.5. Incorporation of rNMPs opposite 8-oxo-G

Despite their specificity, replicative Pols incorporate rNMPs during DNA replication to a very significant extent [81–84]. Estimates range up to 1′000′000 rNMPs being incorporated during the replication of a mammalian genome. While such rNMP incorporation can serve in assisting discrimination between the templating and the newly synthesized DNA strand for certain repair purposes (*e.g.* mismatch repair [85,86]), the presence of less stable rNMPs in DNA constitutes a serious threat to genome stability. This is mainly due to the sugar backbone of RNA being much more prone to strand breakage compared to DNA, which can potentially result in accumulation of strand breaks in such a DNA-RNA hybrid molecule.

While several groups have addressed the propensity and selectivity of different Pols to incorporate rNMPs opposite canonical DNA bases mainly in the context of replication (reviewed in [87]), a very interesting twist to the plot comes from several studies that have assessed the incorporation of rNMP opposite 8-oxo-G. Analysis of Pol4 from *S.pombe* revealed that this enzyme bypasses 8-oxo-G lesions almost exclusively through insertion of rATP, generating a rA:8-oxo-G base pair, which becomes substrate for efficient removal by RNase H2 [35]. RNAse H2-mediated excision then paves the way for another chance to incorporate correct dCTP opposite 8-oxo-G. This is a very interesting finding, and it remains to be seen whether a similar mechanism operates in human cells as well. Of note, bypass of 8-oxo-G using NTPs was also documented for DinB2, a Y-family Pol from *M. smegmatis* [49]. Using human enzymes, a study that compared the rNMP insertion fidelities of Pols β and λ opposite 8-oxo-G found that both Pols were capable of inserting rNMPs both opposite the cognate undamaged templating bases as well as opposite 8-oxo-G [88]. The insertion fidelity opposite 8-oxo-G however differed between the Pols and depended on the template. While Pol λ still preferentially inserted rCMP opposite 8-oxo-G as opposed to rAMP in a substrate mimicking a 1-nucleotide gapped BER intermediate, this preference was entirely lost when a substrate without downstream primer was provided, suggesting that the DNA template influences selectivity of Pol λ in this scenario. Pol β on the other hand showed lower selectivity than Pol λ for incorporation of rCMP *versus* rAMP opposite 8-oxo-G in a 1-nt-gap, whereas it showed better bypass fidelity in a non-gapped template than Pol λ. Incorporation of ribonucleotides opposite 8-oxo-G impaired the functions of both OGG1 and MUTYH, thus potentially impairing 8-oxo-G repair. Finally, experiments with cell extracts of wild-type and knockout cells to repair the gapped template then demonstrated that Pol β was the main responsible for incorporation of rCMP opposite 8-oxo-G. Thus, an additional problem for dealing with 8-oxo-G comes from incorporation of rNMPs opposite the lesion, which can influence the repair activities downstream quite substantially. In a follow-up study, it was shown that Pol η can incorporate rCMP opposite 8-oxo-G and different other damaged guanine products, an activity which was enhanced by its auxiliary factor PolDIP2 [89]. Subsequent removal of ribonucleotides by RNAse H2 was less efficient for rCMP and rGMP than the other ribonucleotides, and rCMP opposite DNA lesions further reduced RNAse H2-mediated ribonucleotide removal. Experiments using cell extracts indicated that translesion synthesis by Pol η can contribute to accumulation of rCMP in the genome, particularly opposite modified G products. It will be of high interest to further elucidate the differential contributions of the various Pols to incorporation of rNMPs opposite damaged bases, and to understand the repair mechanisms in place.

5. Regulation of the key players in 8-oxo-G repair

5.1. Keeping the balance: too little versus too much

Levels of BER proteins can vary considerably between different tissues and individuals [90]. Precise regulation of BER proteins is of paramount importance to genetic stability, as demonstrated by various lines of evidence (Fig. 6). To support efficient and error-free cellular transactions, BER proteins have to be available at sufficient levels to repair DNA damage within a reasonable amount of time. If levels of BER proteins are too low or their activity is too weak to deal with damage present in the cell, this has a negative impact on genome stability and cell viability. Indeed, mutations that affect either protein amounts or the enzymatic activity of BER proteins lead to a reduction in cell viability, an increase in genomic instability and can lead to cancer [91–95]. On the contrary, while too little repair activity is not optimal, too much of it can also be detrimental. Pols that specifically evolved to perform DNA repair, so-called repair Pols, intrinsically harbour a much lower fidelity for DNA synthesis compared to replicative Pols. This is due to their active sites having adapted to accommodate a wide variety of different damaged bases, so that they are capable of dealing with unconventional base pairings [22]. If let loose on long undamaged stretches of DNA, these repair Pols could cause many point mutations by mis-incorporation of nucleotides because of their less stringent 'quality criteria and quality control' for correct base pairing of undamaged DNA bases. Indeed, it has been shown that Pol β can interfere with synthesis of the lagging strand, which leads to lowered replication fidelity [96]. Also, overexpression of Pol β in cells increases their sensitivity to genotoxic treatments, such as ionizing radiation and surviving cells display a hypermutator phenotype [97]. Further support for this hypothesis comes from various reports that show deregulation of

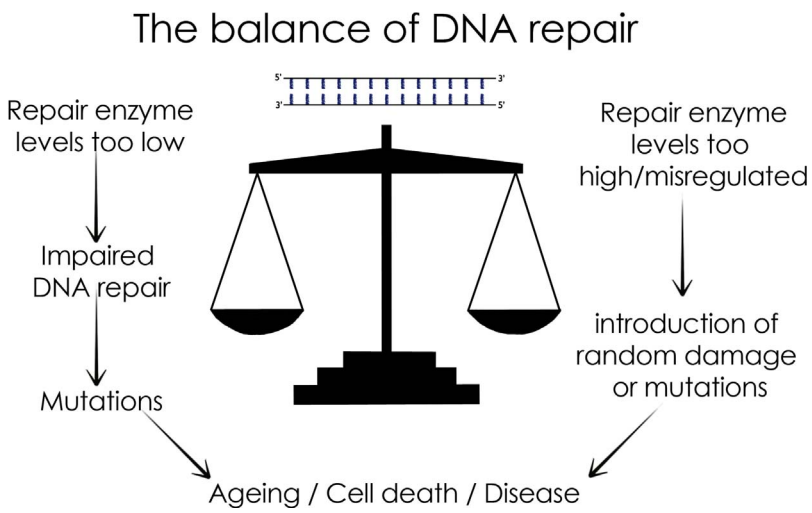

Fig. 6. The importance of correctly balancing DNA repair. (left) inadequate protein levels or hampered enzymatic activity of DNA repair enzymes lead to impairments in DNA repair. A direct consequence of insufficient DNA repair is the accumulation of mutations in DNA, which contributes to the onset of ageing, cell death as well as disease. (right) when DNA repair protein levels are too high or the enzymes overactive due to misregulation, they can interfere with normal cellular DNA transactions, such as *e.g.* DNA replication. This can cause introduction of random DNA damage or mutations, and in turn lead to the onset of ageing, cell death as well as disease. It is therefore highly important to keep the DNA repair activities under tight control and closely adapted to the cellular need.

different repair Pols, including Pols λ and β, can lead to diseases in general, and cancer in particular [98,99]. Interestingly, it has been shown that repair Pols are overexpressed in many tumours, and might thus contribute to disease manifestation [100]. Thus, these important repair enzymes have to be under tight control to guarantee that they only are active when really needed. While such tight regulation is of utmost importance for Pols involved in DNA repair, the same principle can in effect be extended to the entire BER pathway. In summary, it is important for cells to fit their BER capacity to their individual need, as a mismatch between supply and demand can result in compromised viability or induction of mutations. Considering all these facts, it seems nothing but logical to infer that levels of BER proteins should undergo constant adjustment to fit individual needs in response to the cellular environment.

Slowly, regulatory mechanisms controlling BER enzymes are beginning to be revealed. In general, there are several different features that a cell can modulate to control (not only) BER components: abundance, activity, and subcellular localisation. In the following, the most important points about the regulation of key players involved in repair of 8-oxo-G will be summarised.

5.2. Regulation of OGG1

The regulation of OGG1 has been widely investigated by multiple approaches. Mechanisms include regulation of protein activity, protein turnover, and subcellular localization, and some of these features are influenced by posttranslational modifications, such as acetylation and phosphorylation. Additionally, there are plenty of sometimes conflicting reports about transcriptional control of OGG1 upon exposure to genotoxic treatments. A thorough review of these mechanisms contributing to regulation of OGG1 can be found in [1]. More recent evidence can be added to the picture, as discussed in the following. Transcriptional up-regulation of OGG1 has been shown to be triggered by different signalling molecules, such as: 5′-AMP-activated protein kinase (AMPK) activated by rapamycin-mediated inhibition of mammalian target of rapamycin (mTOR) [101], activation of the oxidative-stress responsive transcriptional activator nuclear factor erythroid 2-related factor 2 (NRF2) [102,103], as well as the transcription factor Nuclear transcription factor Y subunit alpha (NF-YA) (*e.g.* [101,104,105]). Also, Breast cancer susceptibility gene 1 (BRCA1) has been implicated in transcriptional regulation of OGG1 [106]. And interestingly, levels of OGG1 have recently been shown to be subject to circadian modulation [107]. In a group of 15 healthy volunteers, the authors found higher levels of OGG1 in the morning compared to the evening, which went in hand with 8-oxo-G repair activity as well, and a significant shift was found in a group of shift-workers experiencing a deregulation of circadian clock genes compared to the control group. These results suggest, that circadian modulation of 8-oxo-G repair by control of OGG1 levels could influence the susceptibility to oxidative stress at different points during the day, hinting at yet another layer of complexity in regulating DNA repair of oxidative damage.

To conclude, OGG1 can be regulated on many different levels, and the inducibility of OGG1 transcription through oxidative or other stress seems to be somewhat tissue- and cell-type specific. More insights on the exact orchestration of how to fit the supply of this important DNA glycosylase to the specific cellular needs will be much appreciated.

5.3. Regulation of MUTYH

The DNA glycosylase MUTYH is a protein that is regulated in a cell-cycle dependent manner, reaching a maximum in S-phase, and co-localizing together with PCNA to replication foci [108]. This obviously S-phase dependent expression and localization pattern was corroborated by a 14-fold higher repair efficiency by using a replication-proficient DNA substrate compared to a non-replicating one [109]. Adjustment of MUTYH levels to cellular needs has been described to be achieved by transcriptional regulation as well as regulation by posttranslational modifications, either leading to a change in its glycosylase activity or its affinity to bind DNA. The details on these regulatory mechanisms have been thoroughly reviewed in [56]. More recently, MUTYH protein levels were found to be directly regulated by the E3 ligase Mule, mediating poly-ubiquitin-chain addition to MUTYH to orchestrate its proteasomal degradation [110].

It is interesting to note that the E3 ligase targeting MUTYH for proteasomal degradation is also the one involved in the decay of its close ‘collaborator’ Pol λ (see Section 5.6 about regulation of DNA polymerase λ). Also, the cell-cycle dependence of MUTYH levels and activity is in perfect alignment with its cellular role in processing A:8-oxo-G mismatches, that result mainly from DNA replication across 8-oxo-G lesions, as discussed above. Given the clear replication-associated role of MUYH, underlined by its co-localization with PCNA to replication foci, and its interaction with components of the replication machinery, like PCNA, MSH2/MSH6 and RP-A, it would be interesting to know more about the exact orchestration of A:8-oxo-G excision during replication and/or repair. Further insights into the mechanism of regulation of this pivotal protein for A:8-oxo-G repair would certainly advance our understanding of how exactly cells deal with the mutational threat posed by 8-oxo-G.

5.4. Regulation of APE1

The endonuclease APE1 is attributed to be responsible for most of

the AP-site cleavage activity taking place in mammalian cells [111,112]. While this makes APE1 an essential enzyme for BER, the flip side of the coin is that APE1, which is an extremely active enzyme, is responsible for the generation of the majority of SSBs produced in the wake of BER [113]. This suggests that APE1 activity requires to be strictly matched with following repair by the core BER complex to resolve any SSBs that are produced by APE1 in a timely fashion. Loss of such thigh regulation of the BER pathway has been suggested to be linked with genomic instability [114,115]. Indeed, increased levels of APE1 have been shown to induce genomic instability, most probably through a lack of coordination with downstream BER activity and resulting generation of an overload of SSBs [116,117]. Furthermore, the connection between APE1 levels and tumour aggressiveness and prognosis is well established (reviewed in [118,119]). Thus, precise regulation of APE1 levels seems to be of high importance for genetic integrity.

APE1 is regulated at many different levels: modulation of APE1 transcription, changes in its subcellular localization (*e.g.* from the nucleus to the cytoplasm), and by modulation of its posttranslational modifications, which in turn can impact on subcellular localization, activity and/or protein stability (reviewed in [120–122]). For instance, ATF4-dependent transcriptional regulation of APE1 upon arsenite exposure of cells has been reported [123], and H2O2-inducible transcription of APE1, among other BER enzymes, was suggested to be mediated by BRCA1 [106]. Also, PARP1 was implicated in control of mitochondrial repair proteins, among which MUTYH and APE1, by localizing to the promoter regions and exerting epigenetic control [124]. Furthermore, p53 was demonstrated to mediate down-regulation of APE1 transcription after genotoxic stress in the form of camptothecin treatment [125]. Similarly, it has been recently shown that a p53-mediated transcriptional control mechanism acting *via* destabilization of the transcription factor Sp1 allows the adjustment of APE1 levels to the load of DNA damage present in cells [126]. The APE1 protein pool can be controlled by the E3 ubiquitin ligase UBR3, which poly-ubiquitinates APE1, thus targeting it for proteasomal degradation [117]. Among control mechanisms of subcellular localization of APE1 S-nitrosoglutathion, a S-nitrosating agent, was found to efficiently promote export of APE1 from the nucleus to the cytoplasm by way of modification of Cys93 and Cys310 of APE1, thus possibly inhibiting its DNA-dependent activities [127]. Furthermore, nucleophosmin was shown to modulate APE1 enzymatic activity [128]. Finally, as a cellular redox factor, APE1 itself can also regulate the levels and activity of other DNA repair proteins, as it can modify several downstream transcription factors (reviewed in [129]).

Thus, control of APE1 is a multi-layered, complicated process far from being completely understood. This befits the general notion that a tight control of this important enzyme has to be exerted to ensure cellular health.

5.5. Regulation of DNA polymerase β

In general, Pol β is viewed as being constitutively expressed – akin to a “housekeeping” enzyme – in most cells [130]. This is perfectly in line with its role as the ‘canonical BER Pol’ whose activity is required in many different scenarios all throughout the cell cycle to ensure repair of abundantly occurring small base lesions and SSBs. While transcription of Pol β has been reported to be inducible in response to certain types of exogenously applied DNA damaging agents (*e.g.* [131]), other authors question whether expression of BER components is inducible (*e.g.* [126,132,133]). It is probably reasonable to assume that the inducibility of Pol β is much dependent on the tissue and cell type, akin to OGG1.

Apart from transcriptional control, precise control of Pol β steady-state protein levels, and in fact the entire core BER complex, is achieved using an elegant multi-layered mechanism that links protein levels with levels of endogenously occurring DNA damage and entails multiple levels of control. Pol β can be bound in a repair-proficient core complex with XRCC1 and Lig III in cells [134]. Importantly, the stability of this protein complex is determined by the presence of the scaffolding protein XRCC1, a reductions in XRCC1 levels (*e.g.* by siRNA or by genetic ablation) lead to reductions in the levels of Pol β and Lig III [115,132,134,135]. Superfluous BER proteins not bound in a complex are targeted by two different E3 ubiquitin ligases called Mule/ARF-BP1 and CHIP: firstly, Mule adds a monoubiquitin to ‘prime’ the protein for subsequent ubiquitination and, secondly, CHIP extends this ubiquitin chain, thus labelling the target for proteasomal degradation [134,136]. Interestingly, the activity of Mule can be inhibited by the tumour suppressor ARF, which accumulates in response to DNA damage [137,138] by a transcriptional regulation through a PARP1-SIRT1-E2F1 axis [132]. Inhibition of Mule activity by ARF binding results in accumulation of active Pol β – XRCC1 – Lig III complexes able undertake DNA repair. A subsequent drop in DNA damage load due to repair results in turn in reduced ARF transcription, activating the Mule-dependent degradation of superfluous BER complexes. Additionally, Mule undergoes constant self-ubiquitination, which targets it for proteasomal degradation. This can be counteracted through USP7S-dependent deubiquitination under physiological circumstances, thus preventing Mule from degradation and enabling it to orchestrate the degradation of Pol β in turn. Upon DNA damage, USP7S is down-regulated, which leads to destabilisation of Mule and subsequent stabilisation of the BER complex [139].

Summarizing, though considered a constitutively expressed protein, steady-state Pol β levels get constantly adapted to the cellular need by matching the supply to the demand, which in turn is determined by the amount of DNA damage that is present in the cell. This fine-tuning ensures that the core BER complex is available at sufficient levels to optimally perform its job, while still keeping a tight regulation to avoid exaggerated activity.

5.6. Regulation of DNA polymerase λ

Initial investigations into the mechanism that regulates Pol λ levels started with the identification of the S-phase kinase complex cyclin-dependent kinase 2 (Cdk2)/Cyclin A as novel interaction partner for Pol λ [140]. Cdk2/Cyclin A was found to phosphorylate Pol λ mainly in the S, G2 and M-phase of the cell cycle. Phosphorylation occurred at four distinct residues and was shown to lead to stabilization of Pol λ by protecting it from degradation *via* the ubiquitin-proteasome system [141]. Subsequently the two E3 ligases CHIP and Mule were identified as capable of ubiquitinating Pol λ *in vitro* [142]. While the relevance of CHIP-mediated ubiquitination of Pol λ *in vivo* remains to be clarified, it was confirmed that Mule is responsible for ubiquitin-dependent degradation of Pol λ in cells [143]. In contrast, while not changing the enzymatic nucleotide selectivity towards 8-oxo-G [122], phosphorylation of Pol λ by Cdk2/Cyclin A leads to a recruitment of Pol λ to chromatin by enhancing its interaction with chromatin-bound MUTYH to form active 8-oxo-G repair complexes. S-phase recruitment of Pol λ to chromatin was even increased upon oxidative stress, suggesting that this mechanism is in place to guarantee the availability of productive repair complexes at the exact time that A:8-oxo-G mismatches are being produced: during replication.

It is interesting to note that, like its ‘partner’ MUTYH (discussed above in Section 5.3), Pol λ seems to be primarily needed on chromatin during S-phase, while its close relative, Pol β, is considered more of a housekeeping enzyme active all through the cell cycle. Thus, a picture slowly emerges in which Pol λ has at least two distinct roles during the S-phase: firstly, it helps the replication fork to correctly bypass 8-oxo-G lesions by engaging in a polymerase switch with replicative Pols (discussed in Section 4.4 and Fig. 4D), and secondly, together with MUTYH it is responsible for correction of erroneous A:8-oxo-G mispairs that have been produced during replication (discussed in Section 4.1 and Fig. 5).

5.7. Regulation of XRCC1

It is interesting, that while Pol β is often considered a housekeeping enzyme, the protein partner that supports its stability and activity, XRCC1, is usually not put into this same category. Indeed, transcription of XRCC1 was reported to be enhanced following DNA damage upon ionizing radiation, as well as *via* EGF signalling through the EGFR and MAPK pathways [144,145]. Furthermore, an MMS-triggered up-regulation of XRCC1 transcription *via* E2F1 has been documented [146]. E2F1 has also been reported to regulate XRCC1 levels in context of the cell cycle [147]. While the basal levels of XRCC1 were reported to be under the control of PI3K-AKT, induction of XRCC1 expression after ionizing radiation was suggested to be MKK1/2-ERK1/2 dependent in A549 cells [148]. On the contrary, low doses of ionizing radiation did not seem to induce XRCC1 expression in TK6 cells [133]. Chk2-mediated stabilisation of the fork-head box M1 (FoxM1) transcription factor was shown to promote transcription of XRCC1 in response to DNA damage by etoposide, IR or UV [149].

XRCC1 can be post-translationally modified by phosphorylation, SUMOylation, poly-ADP-ribosylation and ubiquitination. Phosphorylation of XRCC1 by Casein Kinase 2 (CK2) was shown to be essential to enable the assembly and activity of XRCC1-repair complexes and promote its dissociation from DNA [150–154]. Mutation of the site of poly-ADP-ribosylation protects XRCC1 from ubiquitination and thus proteasomal degradation [154]. Moreover, XRCC1 is SUMOylated [155] and ubiquitination of XRCC1 by the E3 ligase CHIP leads to proteasomal degradation of the protein [134,135,156,157]. Phosphorylation of XRCC1 was found to be prerequisite for such poly-ubiquitination [154]. Finally, interactions of XRCC1 with aprataxin [158], PNKP [159] as well as HSP90 [135,160] were reported to stabilize the XRCC1 protein.

Taken together, there are quite a few reports investigating the regulation of XRCC1 levels in the cellular context, but we are still far from understanding completely all intricacies of its regulation and how it is related to tissue- or cell type and state.

5.8. Regulation of DNA ligases I and III

Details on the regulation of DNA ligases I and III have been thoroughly reviewed in [161]. Mechanisms include transcriptional regulation upon genotoxic treatments (*e.g.* [162]), regulation of its activity and protein partner binding by phosphorylation (*e.g.* [163–165]) and dephosphorylation (*e.g.* [166]), and poly-ubiquitin mediated proteasomal degradation [134,167].

5.9. Regulation of nucleotide pool sanitization enzymes

Except for MTH1, there is no data on regulation of the levels of the other nucleotide pool sanitization enzymes MTH2, MTH3 or NUTD5. For MTH1, intracellular localization of the protein is dependent on its isoform and alternative splicing (reviewed in [168]). Despite the fact that higher levels of MTH1 have generally been observed in cancerous cells compared to normal cells (discussed in [169]), the cell cycle or proliferation rate of cells was not found to influence activity of MTH1 [169]. The up-regulation of MTH1 in cancer cells was thus suggested to be a result of increased oxidative stress in cancer cells [170]. Indeed, up-regulation of MTH1 on mRNA, protein as well as its activity level has been described after exposure of cells to different agents that induce oxidative stress, as discussed in [171]. Furthermore, it was even shown that 8-oxo-G in complex with OGG1 (representing the product of OGG1-mediated 8-oxo-G excision from DNA) is capable of inducing transcription of MTH1, but not MTH2 [172]. It thus seems that cells are capable to regulate the availability of MTH1 in response to the levels of oxidation stress within reasonable limits.

Concluding, regulation of the different key proteins involved in repair of 8-oxo-G is diversified and highly complex. Frequent differences in findings regarding inducibility of transcripts or protein levels might well be due to differences between cell and tissue types, cell cycle stages, use of primary *versus* transformed cells as well as culturing conditions, which could have huge impacts on the baseline levels of DNA damage and the concomitant level of response towards the respective treatments. Clearly, the field would profit from deeper analysis of some of these issues.

6. 8-oxo-G repair in the cellular context

One important aspect of regulation of repair activity that has not addressed so far is the influence of chromatin remodelling on the activity of BER in general, and repair of oxidative DNA damage in particular.

If DNA was simply an elongated loose molecule freely floating in the cell, DNA repair of any particular region would be easily feasible anywhere anytime, provided that the right proteins would find their substrate in an orderly fashion. However, within the nucleus, DNA is never present as a linear molecule. Instead, it is highly organized into a complex structure called chromatin that consists of DNA, histones and many other proteins forming complexes that guarantee the correct spatial and structural arrangement of this huge, compact molecule. Most probably, this complex arrangement of DNA actually also is a prerequisite for correct execution of DNA maintenance and transactions, making sure that factors working together are targeted to the right sequences at the right time. Due to the complexity of this structure, it seems nothing but logical that the accessibility for DNA repair complexes in general, and BER of oxidative DNA damage in particular, can be modulated by different chromatin configurations. Indeed, there is evidence that chromatin remodelling mediated by the de-ubiquitinating enzyme USP7 is important for BER of oxidative lesions, as transient USP7 knockdown did not change the levels or activity of BER enzymes, but significantly reduced accessibility and consequently the repair rate of oxidative lesions [173]. Not only the chromatin status but also the cellular differentiation state seems to play a role in determining its capacity for oxidative BER, as shown in a study using undifferentiated embryonic stem (ES) cells or ES cells differentiated for 0, 4 and 7 days [174]. Amounts of 8-oxo-G and expression levels of OGG1, MUTYH and MTH1 in the cells were measured after H2O2 treatment. While levels of MTH1 and MUTYH remained unchanged, the amounts of OGG1 decreased with increasing differentiation, which was concomitant with an accumulation of 8-oxo-G in those cells, suggesting ES cells were more resistant to oxidative stress than differentiated cells. While the question how BER is organised in the context of chromatin *in vivo* clearly holds high relevance, there seem to be more questions than answers at the current point in time. Recent reviews of literature regarding the interplay between chromatin remodelling and BER, along with a discussion of the complications that arise with the study of this subject, can be found in [175,176].

Another area of research focuses on the occurrence and repair of oxidation damage in telomeric DNA, the extremities of chromosomes. OGG1 was also found to repair 8-oxo-G lesions occurring in the G-rich telomeric DNA by BER, and ablation of OGG1 in *S.cerevisiae* led to an increase in 8-oxo-G in telomeric DNA and induced telomere lengthening by telomerase/Rad52 mediated homologous recombination [177]. These results suggested that 8-oxo-G could disturb telomere length equilibrium by interfering with telomere length maintenance, which may be one of the mechanisms by which oxidative stress damages the genome. Another report analysed the influence of 8-oxo-G repair by OGG1 on mammalian telomeres in *ogg1 -/-* mouse tissues and primary MEFs under various oxidative culturing conditions [178]. Cultivation at 3% oxygen, assumed to be hypoxic conditions, led to telomere lengthening, whereas telomeres shortened in hematopoietic cells and primary MEFs when cultivated in the presence of an oxidant or under normoxic conditions (20% oxygen). Other abnormalities, such as telomere length abnormalities, telomere sister chromatid exchanges,

increased telomere SSBs and DSBs, and others were observed, indicating that 8-oxo-G damage that arises in telomeres, can affect proper telomere maintenance. Similarly, a study examining the susceptibility of telomeric DNA to oxidative base damage demonstrated telomeric TTAGGG repeats to be more prone to oxidative base damage and repaired less efficiently than non-telomeric TG repeats *in vivo* [179]. The activity of OGG1 was similar in telomeric and non-telomeric double-stranded substrates and not impaired by telomere repeat binding factors Trf1 and Trf2. However, in certain specific telomeric structures, 8-oxo-G was less effectively excised by OGG1, depending on its position within these substrates. Collectively, these data indicated the sequence context of telomeric repeats and certain telomeric configurations to contribute to telomere vulnerability during oxidative DNA damage processing. Telomeric DNA can form quadruplex DNA structures *in vitro* and possibly also *in vivo*. One report suggested that the two glycosylases NEIL1 and NEIL3 are capable of removing a variety of oxidative DNA lesions from telomeres and other quadruplex DNA containing contexts [180]. Both glycosylases did not show activity to remove 8-oxo-G from DNA, however. A follow-up of this work confirmed that, in contrast to other oxidative lesions, 8-oxo-G could not be removed from telomeric quadruplexed DNA by either NEIL1, NEIL3 or OGG1, but all three NEIL glycosylases readily excise damage from telomeric and promoter DNA quadruplex structures [181], suggesting that these glycosylases might be involved in both maintenance of telomeres as well as gene regulation. Interestingly, while oxidative DNA damage was shown to be completely repaired in the rest of the genome, it was found to persist in telomeric regions of human primary fibroblasts, and to induce significant temporary telomere shortening as well as increased chromosomal instability within 48 h after oxidative stress, which was restored to almost normal values subsequently [182]. These results suggested a correlation between oxidative DNA damage, telomere length, and abnormal nuclear morphologies induced by chromosome instability. Moreover, 8-oxo-dGTP insertion by telomerase was shown to terminate further elongation of the telomere, while presence of 8-oxo-G in the telomere sequence promoted telomerase activity through destabilisation of the G-quadruplex DNA structure [183]. Thus, the mechanism by which 8-oxo-G is introduced into telomeres seems to dictate its biological outcome in the context of telomere lengthening or shortening. Overall, these results highlight the vast differences of sequence and structure context, chromatin context and biological outcomes of 8-oxo-G in DNA, and warrant future studies to further elucidate the contribution of 8-oxo-G in physiological and pathological states *in vivo*.

7. 8-oxo-G as an epigenetic-like regulator

Presence of DNA damage in a gene can significantly modulate its expression by either directly interfering with transcription or as a consequence of interference between attempts to repair the damage that clashes with transcriptional activity [184]. While 8-oxo-G in DNA has so far been viewed mainly in the light of being pro-mutagenic and thus potentially detrimental to cells, more recent research has also uncovered a more physiological aspect of 8-oxo-G presence in DNA in the control of gene transcription.

8-oxo-G in template DNA was shown to stall transcription by RNA Pol II [185]. Also, a single 8-oxo-G located in the non-transcribed DNA strand of a reporter gene was shown to have a strong negative effect on transcription, suggesting that induction of transcriptional silencing serves ubiquitously as a mode of biological response to 8-oxo-G in DNA [186]. On the other hand, several reports demonstrated that 8-oxo-G induced by oxidative stress could go in hand with increased gene expression [187,188]. Further work then unveiled that 8-oxo-G localized in the promoter regions of various genes could cause a transcriptional increase *via* the BER pathway [189–191]. Thus, it seems as though 8-oxo-G may have a regulatory role in cells undergoing oxidative stress and thus display “epigenetic-like” features in regulation of gene transcription. Indeed, by studying the exact location of 8-oxo-G in mouse embryonic fibroblasts through sequencing, regulatory gene elements such as gene promoters and un-translated regions were found to contain more 8-oxo-G enriched sites than expected to occur by stochastic distribution of the damage, further underlining the possible role of 8-oxo-G in epigenetic modulation of gene transcription [192]. For more details on this topic, the interested reader is referred to an excellent recent review [193].

These findings again demonstrate that most things in biology have at least two sides: in the case of 8-oxo-G this seems to be a balance between pro-mutagenic aspects, weighed up against possibly beneficial gene regulatory roles.

8. Relevance of oxidative stress and 8-oxo-G repair to disease

There has been a longstanding association between oxidative stress and oxidative DNA damage with a wide variety of different human disorders, ranging from cancer, various neurodegenerative and neurodevelopmental disorders, inflammatory disorders to ageing (*e.g.* reviewed in [69,194–198]). Though for many of these associations the initiating quality of oxidative stress on the onset of the disease is still not absolutely proven, oxidative stress – and with it oxidatively damaged DNA – clearly seems to play a major role at least in disease progression. Interestingly, oxidative stress and ROS are not only thought to promote the development of cancer through generation of mutations, but more recently it emerges that ROS have a quite central role in cell growth signalling by influencing mitochondrial metabolism, cellular proliferation as well as cellular stress responses (reviewed in [195]). Indeed, ROS have been found to be an integral part of many physiological signalling pathways, which can have just as important a role in contributing to pathogenesis as direct mutations. Therefore, it is reasonable to assume that the role of ROS in pathogenesis of many different disorders is a complex interaction between direct mutations and activation of a variety of different cellular pathways [199,200]. While these redox-signalling properties of ROS are highly interesting, the focus of this review is on DNA damage, which is the reason that this discussion remains restricted to ROS-generated mutations in DNA.

Single nucletoide polymorphisms (SNPs) in genes can cause a change in the activity of a protein, either directly through structural changes or for instance by alterations in its binding with interaction partners, its expression, subcellular localisation or stability. For obvious reasons, if such a change occurs in a DNA repair protein, this might cause a build-up of DNA damage or mutations that in turn can precipitate the development of pathologies. Indeed, a plethora of polymorphisms in many different DNA repair enzymes have been reported, some of which were suggested to be associated with a propensity for cancer development or been tied to the onset of neurodegenerative diseases. While the data are quite clear on a very few select genes in specific pathologies, for the majority of the proteins that are discussed in the following the impact of the different polymorphic variants to human disease remains to be unequivocally proven. Due to the many – often conflicting – epidemiological analyses and meta-analyses available I will not go into detail on every single reported polymorphism, but rather try to focus on the more consolidated facts regarding findings from *in vivo* studies using animal models or human patient samples.

8.1. 8-oxo-G repair relevance in vivo

8.1.1. Cancer

Genetic instability is one of the few enabling hallmarks of cancer, and is thus considered indispensable for the development of tumours [201]. It is therefore not surprising that oxidative stress and oxidative DNA damage, known to lead to DNA damage and mutations, have been intimately linked with cancer initiation and progression. Indeed, elevates levels of ROS, and concomitant oxidative DNA damage have been reported in almost all types of cancer, and manipulations of ROS levels are being discussed as potential anticancer strategies (reviewed in

Table 3
BER proteins and their knockout phenotypes.

Protein	KO Phenotype	Refs.
OGG1	Viable, fertile, slight predisposition for tumour development; for details see text	[207,208]
MUTYH	Viable, fertile, slight predisposition for tumour development; for details see text	[211,212]
APE1	Embryonic lethal	[219,220]
DNA polymerase β	Embryonic lethal	[221]
DNA polymerase λ	Viable, fertile	[216]
XRCC1	Embryonic lethal	[222]
DNA ligase I	Embryonic lethal (hematopoietic defects after midterm)	[223]
DNA ligase III	Embryonic lethal	[224]

Table summarizing the BER proteins discussed throughout this manuscript and their knockout phenotype.

[202–204]). Of note, many cancers have been found to harbour C:G → A:T transversion mutations, further underlining the importance of 8-oxo-G in the development of cancer (*e.g.* [205]). C:G → A:T mutations have even been found to be frequent among germline and somatic mutations in both humans and mice [206]. Overall, cancer development, biology and progression and oxidative DNA damage are very tightly related.

To specifically analyse the contribution of 8-oxo-G repair to cancer development in an *in vivo* model, there have been various studies assessing the effect of removing some of the key repair factors involved its repair (Table 3). Investigations into the roles of OGG1 and/or MUTYH *in vivo* using mice with targeted knockouts (KOs) of the respective genes have been recently reviewed in detail [56,69]. In short, OGG1 single-KO mice are viable and fertile, showing normal life span with no major defects that can be observed [207,208]. In these mice 8-oxo-G accumulated in nuclear and mitochondrial liver DNA, and an elevated spontaneous C:G → A:T transversion rates in some but not all tissues was observed. There is possibly a slightly elevated predisposition for lung cancer at 18 months after birth [209]. The apparent lack of 'problems' in mice lacking the major 8-oxo-G removing enzyme OGG1 was slightly astonishing and suggested other backup mechanisms to be in place to compensate loss of OGG1. Very recent data from a multiorgan carcinogenesis bioassay using a variety of known genotoxic carcinogenic agents that observed mice up to 34 weeks suggests however, that OGG1 KO mice might indeed have an enhanced susceptibility for tumour development in a variety of organs [210]. It thus seems that lack of OGG1 can be largely compensated for under physiological circumstances, but this buffering capacity is not sufficient under conditions of heightened threat to genetic integrity. MUTYH single-KO mice proved to be viable, fertile and without major growth defects and normal life span, with a slight predisposition to develop intestinal adenoma and carcinoma at 18 months of age, which can be exacerbated by treatment with oxidative stress inducing agents [211,212]. Again, accumulation of 8-oxo-G was found to be organ dependent. Mice lacking both OGG1 and MUTYH, while viable and fertile, display a reduced life span and a strong predisposition for tumours in lung and ovaries as well as lymphomas [211]. Interestingly, these mice also show an altered behavioural and learning phenotype, which stems from differential gene expression in the brain [213]. Deletion of MTH1 in mice results in a slightly increased mutation rate, with tumours located to lung, liver and stomach [214,215]. Taken together, these findings demonstrate that 8-oxo-G repair seems to be more important in some tissues than others, and that nature has many redundancies or backup mechanisms in place to be able to compensate for the loss of one particular repair system quite extensively. Nevertheless, the results from these animal studies highlight the involvement of 8-oxo-G DNA damage and its repair in the development of cancer.

It has to be mentioned that the KO of other important factors involved in repair of 8-oxo-G, such as APE1, Pol β, XRCC1 Lig I and Lig III is embryonically lethal, which is why studies assessing the impact of these have not been performed (Table 3). Mice that are knockout for Pol λ are viable and fertile, and lack any overt pathologies [216]. To the best of my knowledge, these mice have not been analysed from the perspective of cancer propensity, however. It should also be added here that an initial report on Pol λ knockouts reported these mice to display hydrocephalus, situs inversus and male infertility [217]. However, it is generally thought nowadays that the targeting approach used in this particular study ablated also adjacent parts of DNA other than Pol λ, where genomic analysis predicted the existence of a transcribed gene strongly conserved throughout evolution on the opposite strand, which was most probably responsible for the observed phenotype [218].

8.1.2. Neurodegenerative disorders

There have been long-standing observations of increased oxidative DNA damage, both in nuclear as well as mitochondrial DNA, in *post mortem* samples from human brain regions affected by neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS) and stroke (reviewed in [225,226]). Also, oxidative stress has been linked to trinucleotide repeat (TNR) instability, a hallmark of Huntington's disease (HD) (reviewed in [227]), and others. And finally, increased oxidative DNA damage has also been implicated to play a causal role in neurodevelopmental dysfunctions, such as autism spectrum disorder (ASD) and schizophrenia (reviewed in [198]). Similarly to cancer, the cause-consequence relationship has not been unequivocally established yet for all of these disorders and oxidative DNA damage. Nevertheless, BER of oxidative DNA damage certainly occupies a central role in the pathogenesis of these disorders.

Taken together, there is an abundant amount of literature documenting the involvement of various different BER proteins in human diseases, a short overview of which is purveyed to the reader more in detail in the following sections as well as in an overview in Table 4.

8.2. OGG1 and human diseases

While there are no reports about hereditary deficiencies or inactivation of OGG1 in relation to a cancer predisposition phenotype in humans, somatic mutations and polymorphisms in OGG1 that impact its function have been numerously described in association with a variety of different types of cancer (recently reviewed in [69]). The impact of DNA polymorphisms in OGG1 on cancer risk has been reviewed thoroughly [228]. Given its central role in the removal of 8-oxo-G from the genome, it thus is very likely that OGG1 has a role in prevention of cancer development in humans.

Interestingly, OGG1 has also been linked to the pathogenesis of asthma (reviewed in [196]). Current research points to following mechanism underlying this phenomenon: free 8-oxo-G forms a complex with OGG1 which subsequently activates RAS-family GTPases that lead to an activation of the innate and adaptive immune systems, thus leading to the pathological remodelling found in asthmatic patients. Also other links between OGG1 and diseases involving an inflammatory pathogenesis have been solidified lately (reviewed in [69]). And lastly, changes in OGG1 levels as well as a polymorphism have been associated with neurodegenerative disorders, such as AD, PD, ALS, HD and stroke/ischemia (reviewed in [229]). Recently, a study investigating the expression of a panel of BER proteins in peripheral blood from 100 AD patients and 110 healthy volunteers found significant down-regulation of OGG1 in patients, which was not due to differential methylation of the gene promoter [230,231]. A possible association of SNPs in OGG1 and AD has been identified [232] and these SNPs altered OGG1 catalytic activity and sensitized cells to DNA damage [233].

8.3. MUTYH and human disease

The evidence supporting the importance of correct repair of A:8-

Table 4
Overview of associations of BER-proteins with human disease.

Protein	Associated human diseases
OGG1	- Various cancer types (Polymorphic variants and expression changes) - Asthma - Neurodegenerative disorders (AD, PD, ALS, HD, Stroke/ischemia)
MUTYH	- MUTYH-associated polyposis (MAP) and various other types of cancer (Germline mutations) - Neurodegenerative disorders (PD, Stroke/ischemia, AD, HD and other TNR expansion disorders, Friedreich's ataxia)
APE1	- Various cancer types (levels correlate with tumour aggressiveness) - Neurodegenerative disorders (AD, PD, HD, ALS, Ataxia with Oculomotor Apraxia Type 1, cerebral ischemia)
DNA polymerase β	- Possibly involved in tumour formation (deregulated levels in tumours and evidence for pathogenic polymorphisms) - Neurodegenerative disorders (AD, HD, stroke/ischemia)
DNA polymerase λ	- Possibly involved in tumour formation (deregulated levels in tumours and evidence for pathogenic polymorphisms)
XRCC1	- Various cancer types (deregulated levels in tumours and evidence for pathogenic polymorphisms) - Neurodegenerative disorders (AD, HD, stroke/ischemia, progressive cerebellar ataxia, ocular motor apraxia and peripheral axonal neuropathy) - Epilepsia, Down's syndrome
DNA ligase I	- Various cancer types - TNR expansion disorders
DNA ligase III	- Various cancer types

Table summarizing the BER proteins discussed throughout this manuscript and their associations with human diseases. For references see detailed text sections.

oxo-G mismatches *via* the MUTYH-initiated pathway to prevent human disease has solidified significantly over the last decade. Biallelic germline mutations in MUTYH are known to cause a cancerous disease termed MUTYH-associated polyposis (MAP) (reviewed in [56]). MAP runs in families in an autosomal recessive mode and is characterized by the formation of multiple colorectal adenoma and carcinoma as well as an increased propensity to develop tumours of the ovaries, bladder, skin and breast. MAP cases account for approximately 1% of all colorectal cancer cases. Interestingly, no other genes that are involved in the repair of oxidative DNA lesions have been associated with a multiple colorectal adenoma phenotype thus far [234]. Carriers of biallelic germline mutations in MUTYH were also found to be at higher risk for extracolonic cancer at a variety of sites (*e.g.* [235,236]). Even heterozygous germline mutations in MUTYH have been linked to a elevated risk of colorectal cancer above the age of 55 [237]. Interestingly, tumours from MAP patients show particular features of microsatellite instable cancers similar to those arising from MMR deficiency [238], an observation also seen in B-cell lymphoblastic lymphomas arising in mice that are double-KO for *msh2* and *mutyh* [239]. Further, the expression patterns of human leucocyte antigen I on tumour cells derived from MAP patients was defective in 65% of tested primary carcinomas and often associated with loss of expression of beta-2-microglobulin, which again are features usually observed in MMR-defective tumours [240]. In patients with colorectal cancer, an association of MUTYH and MSH6 germline mutations has been described, suggesting that both genes act cooperatively and a simultaneous deficiency in both might possibly confer an increased risk for development of colorectal cancer [241,242]. These findings were in contrast however to an earlier study that did not find any association between germline mutations of these two genes in hereditary non-polyposis colon cancer patients [243]. Yet another report suggested a possible mutual exclusivity of abrogation of MSH6 and MUTYH in humans [244]. Finally, carriers of mutations in both MUTYH as well as a MMR gene (MLH1, MSH2 or PMS2) were at substantially higher risk to develop colorectal cancer than those carrying MUTYH mutations alone [245]. Concluding, while the final verdict of the interplay between MMR and MUTYH mutations in cancer still awaits confirmation, it seems likely, given all the *in vitro* and *in vivo* data as well as the data from human patients that there is a strong interplay between MMR and MUTYH-initiated BER in handling oxidative DNA lesions, such as 8-oxo-G.

More recently, inactivation of MUTYH through germline mutations has been found to be associated with other types of cancer than colon carcinomas as well, such as breast cancer [246], pancreatic neuroendocrine tumours, but not pancreatic ductal adenocarcinomas [247]. Furthermore, a germline mutation in MUTYH has been associated with small intestinal neuroendocrine tumours [248]. The same study also found an association between these tumours and germline mutations in OGG1, but those results did not reach statistical significance. Of note, all reported tumours with involvement of MUTYH mutations harbour characteristic C:G → A:T mutational patterns, indicative for the importance of the MUTYH-dependent repair pathway that prevents 8-oxo-G-derived C:G → A:T transversions. Germline mutations in MUTYH have also been tied to high-grade pediatric gliomas and pilomyxoid astrocytoma in infancy [249,250], castrate-resistant prostate cancer [251], urinary tract cancer [252]. and non-BRCA hereditary breast and/or ovarian cancer syndromes [253]. And lastly, a very recent analysis of metastatic cancer found presumed pathogenic germline mutations of MUTYH in 10 patients out of a cohort of 500 patients in total with a wide array of different tumour types [254]. This translated to 16% of all 63 presumed pathogenic germline mutations found in the study to be located in the MUTYH gene, a number even higher than that for BRCA2, CHEK2 (both 14%), and BRCA1 (8%). This exciting finding propels MUTYH and its role in familial predisposition to cancer in general, as opposed to being restricted to its hitherto well-known role in colon cancer, into the limelight.

A reduction in MUTYH expression, along with reductions in OGG1 and MTH1, was recently published in a set of 63 cases of diffuse-type adenocarcinoma of the gastric cardia [255], and in a cohort of 50 patients with hepatocellular carcinoma compared to 50 healthy controls [256]. Similarly, MUTYH levels were significantly decreased in about two third of investigated prostate adenocarcinoma compared to non-cancerous prostatic tissue, which led to a significant increase of total somatic mutations as well as C:G → A:T transversions in the MUTYH low expressing group [257]. Altered expression levels of MUTYH were found to correlate with an increase in 8-oxo-G in ulcerative colitis-associated carcinogenesis, suggesting that an increase in MUTYH may contribute to early carcinogenic events in this condition [258]. Indeed, MUTYH was found to influence the inflammatory response in a mouse model of ulcerative colitis, as mice with a MUTYH KO were much more resistant to develop ulcerative colitis and had a much dampened response in cytokine expression than their wild type counterparts [259]. This is in line also with the proposed role of MUTYH in eliminating heavily damaged cells to safeguard the organism against carcinogenesis, as delineated further below [260]. Indeed, MUTYH was shown to have a protective effect against inflammation-induced colorectal carcinogenesis by mediating inflammatory responses that lead to the removal of corrupted cells [261].

Mechanistically, MUTYH malfunction in cancer has been linked to C:G → A:T transversions in genes that are known proto-oncogenes, such as APC, KRAS, or Ctnnb1 and other important cellular targets

[258,262–267]. This finding is in accordance with the well-established role of MUTYH to prevent 8-oxo-G mediated mutagenesis. A very recent analysis revealed significantly more protein-changing somatic mutations, truncating mutations and copy number variants in duodenal adenomas from MAP patients compared to adenomas from patients suffering from familial adenomatous polyposis, another inherited disorder characterised by colorectal polyposis and cancer [267]. The authors thus conclude that MAP patients might thus even be at higher cancer risk in the context of apparently benign disease, which has implications for clinical management of these patients.

Interestingly however, apart from its protective role against mutations, MUTYH is also slowly emerging to be an initiator of programmed cell death in states of oxidative stress to suppress tumourigenesis by driving efficient elimination of cells with high 8-oxo-G levels (reviewed in [260]). This is achieved by transcriptional up-regulation of MUTYH through p53, upon which the heightened cellular MUTYH-incision activity causes an accumulation of SSBs in the nuclear as well as the mitochondrial DNA, which in turn lead to PARP1/MLH1- or calpain-dependent execution of apoptosis, respectively [268]. This pro-apoptotic activity of MUTYH has also been noted with the combination of the UVA photosensitiser 6-thioguanine and UVA, as a deficiency in MUTYH rendered cells (and mice) more resistant to this synergistically cytotoxic treatment regime [269]. Therefore, it seems that MUTYH has a dual role in protecting organisms against tumour formation: on one hand it serves with its DNA repair capacity to avoid mutations from forming, and on the other hand it acts as a 'cellular thermostat' for oxidative DNA damage, which triggers apoptosis upon accumulation of too many DNA lesions. In light of this, it is interesting to note that, to the best of my knowledge, there has not been a single report showing overexpression of MUTYH in cancer.

The involvement of MUTYH in neurological disorders is somewhat less analysed. It has been implicated in PD and stroke/ischemia, but further research is required to solidify this evidence and further our understanding of the role of MUTYH in the brain (reviewed in [229]). Repair of 8-oxo-G lesions by MUTYH was demonstrated to be responsible for triggering neurodegeneration through activation of apoptotic signalling that leads to exacerbated microgliosis, and suggested that suppression of MUTYH during conditions of oxidative stress might confer protection of brain tissue [270]. Recently, a study investigating the expression of a panel of BER proteins in peripheral blood from 100 AD and 110 healthy volunteers found significant down-regulation of MUTYH in patients, which was not caused by differential methylation of the gene promoter [230]. The involvement of MUTYH in initiation of neurodegeneration in the context of AD has been discussed in [271]. Recently, a combination of oxidised dNTP pools and the subsequent repair by OGG1 and MUTYH was shown to cause TNR instability, which is the causal molecular event underlying HD and other TNR expansion disorders [272]. Also, a combined deficiency of OGG1 and MUTYH caused an acceleration in the clinical course of prion disease, suggesting that accumulating oxidative DNA damage might exacerbate the final toxic phase of the disease [273]. And finally, MUTYH was demonstrated to be involved in microglial activation that is initiated by DNA damage in a mouse model of Friedreich's ataxia [274].

8.4. APE1 and human diseases

Data implicating malfunction of APE1 in a variety of human diseases is quite extensive and has recently been thoroughly reviewed recently [275]. For instance, elevated expression of APE1 has been found in many tumours and in many cases seems to be associated with cancer aggressiveness and resistance against chemo- and radiotherapy in a variety of different cancers. The impact of DNA polymorphisms in APE1 on cancer risk has been reviewed thoroughly [228]. Due to the multifunctional nature of the APE1 protein − acting as redox signalling factor as well as a key player in BER, where it is the main responsible for generation of single strand breaks in the cell, it is not surprising that APE1 emerges as a central player in protecting against oncogenic transformation. Other than in cancer, increases in APE1 levels were found to generate microsatellite instability in chronic inflammatory diseases, such as ulcerative colitis [276].

The relationship between APE1 and central nervous pathologies has been rather widely investigated. Changes in APE1 levels can be found in patients with AD, PD, HD, ALS, Ataxia with Oculomotor Apraxia Type 1 and cerebral ischemia (reviewed in [229,275]). Taken together, these findings point to a central role of APE1 in the maintenance of human physiology, reflecting its many different cellular functions. Recently, a study investigating the expression of a panel of BER proteins in peripheral blood from 100 AD patients and 110 healthy volunteers found significant down-regulation of APE1 in patients, which was not due to differential methylation of the gene promoter [230].

8.5. DNA polymerase β and human diseases

Several small-scale sequencing studies have found 30–40% of human tumours of different origins to harbour mutations in Pol β [277,278]. Also, a few polymorphic variants of Pol β have been identified in the human population. The effect of some of these polymorphisms and different mutations found in various cancers have been analysed in more detail. Indeed, some of them can induce DNA damage, mutations or even cellular transformation of cells, suggesting that these mutants can causally contribute to tumour development (reviewed in [279]). More than 2-fold overexpression of Pol β on protein level was found in 29% of all tumour samples compared to matched normal tissue, while lower than 0.5-fold under-expression was found in 20% of all tested tumours. Differential expression of Pol β has also been noted several other studies [280–282]. While most of these results are not able to directly delineate a causal role of mutated or mis-regulated Pol β in cancer pathogenesis in humans, they are highly interesting and further investigations into the subject are warranted.

Apart from cancer, Pol β has been suggested to be involved in the pathogenesis of AD, HD as well as stroke/ischemia (reviewed in [229]).

8.6. DNA polymerase λ and human diseases

Currently, there are 2 single nucleotide polymorphisms in Pol λ that may be associated with breast cancer – T221P and R438W [283]. While there has not been any functional follow-up information on T221P, Pol λ R438W was originally found when screening several normal and tumoural cDNA samples for polymorphisms, and was demonstrated to have a reduced base substitution fidelity, increase the mutation frequency, generate chromosomal aberrations and compromise the homologous repair pathway especially in response to camptothecin treatment [284,285]. Interestingly, another study found this Pol λ R438W to be significantly enriched in the germlines of breast cancer patients [286]. When cells were exposed to estrogen – which induces ROS and thus 8-oxo-G lesions in cells – Pol λ R438W-mediated bypass of 8-oxo-G lesions was not error-free and led to an increase in mutagenesis as well as replicative stress, suggesting that this polymorphism could increase the propensity to develop estrogen-associated breast cancer.

A study investigating mRNA expression levels in 68 untreated samples of different types of cancer found Pol λ to be overexpressed in 24% of the analysed cancers and to be under-expressed instead in 16% of them [100]. Similarly, an analysis of Pol λ levels in the bronchiolar epithelium found a significant correlation between expression of Pol λ and habitual smoking in patients with lung cancer [287]. While intratumoural expression of Pol λ failed to correlate with the smoking status, tumours in heavy smokers that did not express Pol λ were at a significantly more advanced clinical stage. These findings suggested that Pol λ might be involved in the repair of tobacco-smoke derived DNA damage in the respiratory system. Interestingly, cigarette smoke is a complex mixture consisting of over 3′500 harmful compounds, among

which can be found high levels of free radicals and ROS [288]. Indeed, a study found 34% of all identified somatic substitutions to be C:G → A:T transversion mutations in a small cell lung cancer cell line, suggestive of 8-oxo-G mediated mutagenesis [289]. Furthermore, an analysis of 518 protein kinase genes in 210 different human cancers detected 1007 somatic mutations, of which a large part were C:G → A:T transversions, especially in breast, lung and ovarian cancer [205]. Summarizing, there is evidence for a role of Pol λ and its involvement in mitigating 8-oxo-G induced mutagenesis in preventing tumour development, especially in breast and lung tissue.

8.7. XRCC1 and human diseases

As XRCC1 has a key role in coordination of BER, dysfunctions in this protein have been abundantly suggested to be involved in cancer formation. Indeed, an accumulation of unrepaired SSBs, caused *e.g.* through defective or insufficient DNA single-strand break repair, has been suggested to mechanistically cause the very first steps of carcinogenesis [115,290].

The impact of different DNA polymorphisms in XRCC1 on cancer risk has been reviewed thoroughly [228]. On a mechanistic level, one of the most predominant XRCC1 polymorphic variants, R280H, was found to result in increased focus formation in mouse C127 cells and to induce cellular transformation in human MCF10A cells [291]. Indeed, cells expressing this variant had significantly more chromosomal aberrations and double strand breaks, suggesting that individuals carrying this mutation might be at increased risk of cancer development.

Literature addressing the expression levels of XRCC1 in cancer is abundant. Immunohistochemical (IHC) detection found high expression of XRCC1, among some other BER proteins, to correlate with high T-stage (in the TNM staging), to lymph node positivity, and poor disease-free survival in a total of 142 gastric adenocarcinomas [292]. Similarly, another study using IHC found XRCC1 protein significantly down-regulated in a training cohort of 80 gastric carcinoma, which was tested in a cohort of 374 patients and validated in an independent cohort of 385 patients [293]. However, in contrast to the previous report, this study found XRCC1 levels significantly correlated with overall survival, so that the high XRCC1 expressing tumours had a longer overall survival. Furthermore, the XRCC1 low expressing group significantly profited from platinum-based chemotherapy. Another study addressing 612 specimen of gastric cancer found no significant correlation between XRCC1 expression levels and overall- or disease free survival [294]. However, patients with negative XRCC1 expression seemed to benefit more from platinum-based adjuvant chemotherapy.

High XRCC1 mRNA levels in esophageal squamous cell carcinoma were correlated with longer median overall survival [295]. High mRNA levels of XRCC1 emerged as an independent prognostic factor for ESCC patients using a multivariate analysis. While no association could be found for XRCC1 expression and clinico-pathological features of esophageal squamous cell carcinoma in another study, tumours positive for RASSF1 and negative for XRCC1 were correlated with a longer median overall- and progression-free survival [296].

In a panel of 50 Head and Neck Squamous cell carcinomas (HNSCC) and controls, a statistically significant down-regulation of RNA levels of XRCC1 was found in tumours, and XRCC1 levels were negatively correlated to Ki-67 levels, increased levels of which are indicative of cellular proliferation [297]. Additionally, XRCC1 levels were positively correlated with OGG1 levels in this study.

RNA expression levels of XRCC1, and also OGG1, were significantly lower in a cohort of 75 HNSCC compared to control tissue, and XRCC1 and 8-oxo-G levels were negatively correlated [298]. Further, multivariate logistic regression analysis demonstrated that low expression of XRCC1 an OGG1 was associated with a statistically significant increase in the risk of HNSCC.

Lower expression of XRCC1, quantified by RT-qPCR as well as Western blotting, was found both in 40 samples of squamous intraepithelial lesions (SIL) as well as 50 samples of invasive squamous cell carcinoma of the cervix (CC), as compared to 85 control subjects [299]. By using a multivariate logistic regression analysis, low expression of XRCC1 was significantly associated with an increased risk for both SIL and CC.

An analysis of 1′297 cases of early breast cancer, succeeded by validation in an independent cohort of 281 estrogen receptor α negative breast cancers found loss of XRCC1 expression in 16% of cases, which was significantly associated with high grade, loss of hormone receptors, triple negative tumours and basal-like phenotypes, and a two-fold increase in risk of death as well as poor outcome [300]. Thus, loss of XRCC1 expression seemed to lead to an aggressive phenotype. This study also showed preclinical data of a synthetic lethality between XRCC1 deficient cancer cells and a DNA double-strand repair inhibitor. Further investigation of XRCC1 protein expression in two cohorts of 1620 sporadic and 50 germ-line BRCA1 mutated breast cancer samples, and mRNA expression in 1952 and 249 samples, respectively, revealed that BRCA1 negativity was strongly associated with a low XRCC1 expression both at mRNA and protein levels [301]. In BRCA1 negative tumours, a low expression of XRCC1 was significantly associated with poor survival compared to high XRCC1 expressing BRCA1 negative tumours, suggesting that XRCC1 expression status might have prognostic significance in BRCA1 negative tumours. In contrast, the same group found XRCC1 expression in ovarian tumours to be associated with higher disease stage and platinum resistance, as well as a two-fold increase in the risk of death [302]. Thus, XRCC1 expression in this setting was associated with adverse clinico-pathological and survival outcomes in patients, and non-platinum-based treatment of XRCC1 positive tumours should be considered. In a cohort of 1′269 breast cancers, and validated in an independent estrogen-receptor α negative cohort of 279 cases, XRCC1 low-expressing patients had high numbers of $CD8^+$ tumour-infiltrating lymphocytes, but were also significantly linked to higher grades, proliferation indexes, presence of dedifferentiated cells and poor survival [303]. Furthermore, PD-1^+ or PD-$L1^+$ breast cancers that displayed low XRCC1 were more aggressive, suggesting an interplay between DNA repair and immune checkpoints in the biology of breast cancer. Interestingly, a study analysing 40 women with newly diagnosed breast cancer, of which 20 had acute side-effects after radiotherapy and 20 did not, found that XRCC1 levels were significantly lower in the group with acute side-effects [304]. These results suggested that a decrease in XRCC1 might be associated with an increased risk of radiotherapy-induced acute side effects in breast cancer patients.

Non-small cell lung cancer (NSCLC) patients with low XRCC1 mRNA levels were found to have a higher response rate to chemoradiotherapy compared to those with high expression levels [305].

IHC analysis of 157 locally advanced bladder cancer samples that had received combined trimodality therapy found that patients positive for XRCC1 expression exhibited significantly better disease-specific survival rates [306]. Measurements of XRCC1 mRNA levels in 52 specimen of primary urothelial carcinoma of the bladder found increases in XRCC1 significantly associated with higher grade tumours [282].

IHC assessment of XRCC1 expression on a tissue microarray with 119 melanoma samples, loss of XRCC1 was associated with progression of the disease (from dysplastic nevi to primary and metastatic melanoma) [307]. XRCC1 loss further also correlated with worse overall and disease-specific 5- and 10-year survival.

High nuclear expression of XRCC1, determined by IHC of 160 biliary tract cancer samples, was much lower in neoplastic tissues than control tissues [308]. Furthermore, high nuclear expression was found to positively correlate with overall survival, and patients with high cytoplasmic expression of XRCC1 had significantly more lymph node metastasis and a worse overall survival, and more vascular invasion could be seen in low nuclear expressing cases.

And finally, XRCC1 mRNA levels were found to be significantly lower in hepatocellular carcinomas than control tissues [256].

In conclusion, while there is a plethora of data regarding XRCC1 expression levels in many different types of cancer, there is still a lack of complete understanding as to what extent and how XRCC1 levels correlate with disease progression. Future investigations will hopefully bring clarification to its exact role in carcinogenesis.

The involvement of XRCC1 in neurological diseases has garnered a bit less attention than is connection to cancer, however there is a variety of very interesting findings regarding this connection which have mostly been reviewed in [229]. Brain-specific KO animals for XRCC1 (driven by Nestin-Cre) show age-dependent accumulation of DNA damage, loss of cerebellar interneurons and altered hippocampal homeostasis [309].

Changes in XRCC1 levels have been associated with AD, models of HD, stroke/ischemia and epilepsia, as well as in brains of Down's syndrome patients (reviewed in [229]). Similarly, a partial loss of XRCC1 was shown to result in increased brain damage and impaired recovery from ischemic stroke in a mouse model [310]. By far the most convincing report of XRCC1's importance in development and maintenance of the central nervous system comes from the Caldecott lab, which identified the first ever reported patient carrying a biallelic mutation in XRCC1 that almost completely deletes the protein, most likely by triggering nonsense-mediated mRNA decay through premature stop codons [311]. These mutations are associated with progressive cerebellar ataxia, ocular motor apraxia and peripheral axonal neuropathy.

8.8. DNA ligases I and III and human diseases

A complete KO of Lig I was found to cause embryonic death at mid-gestation because it is required for fetal liver erythropoiesis [223]. Interestingly, this result suggested that replication can be performed even in the absence of Lig I. Mice with a point mutation in the Lig I gene found in a human cancer patient displayed an increased incidence of a diverse range of spontaneous epithelial tumours, along with replication failure and genome instability [312]. Interestingly, inactivation of Lig III did not cause repair defects in nuclear DNA, but resulted in loss of mitochondrial DNA, suggesting it was dispensable for nuclear DNA repair [313]. Instead, Lig I was critical for nuclear DNA repair, in a cooperative manner with Lig III.

Expression of Lig I, as determined by Western blot of extracts from various human malignant cancer specimen, was found to be elevated in human cancers, suggesting it played an important role in proliferating cells [314]. Lig IIIa, the nuclear isoform of Lig III, was shown to be up-regulated in chronic myeloid leukemia, which possibly contributes to disease progression [315].

Expression patterns of both ligases in the brain have been reviewed in [229]. TNR expansion has been tied to activity of DNA ligase I [316–322].

SNPs of both ligases have been implicated to play a role in cancer and neurodegenerative diseases, but larger validation studies are still missing for conclusive evidence.

8.9. MTH1 and human diseases

To date, no germline mutations of MTH1 have been reported in the context of cancer. Interestingly, an increased expression of MTH1 correlates with malignancy of tumours, suggesting that tumour cells rely strongly on sanitisation of their nucleotide pools for proper growth (reviewed in [72]). Inhibition of MTH1 was proposed as an attractive cancer-drug target [323,324], but this finding has been hotly debated and opposing results have accumulated since [325–327]. Thus, it remains to be established how far cancer cells really rely on MTH1 activity.

In contrast to its involvement with cancer in humans, the role of MTH1 in the protection of brain tissue has been widely analysed. Ties between MTH1 and neurodegenerative diseases, such as Alzheimer's disease [328–330] and Parkinson's disease [331,332] exist, suggesting that MTH1-mediated nucleotide pool sanitisation is important in the protection against various brain pathologies (reviewed in [72]).

9. Conclusions and perspectives

Oxidative DNA damage, and in particular 8-oxo-G has garnered much attention over the last decades. The mechanisms underlying its repair are being progressively unveiled in detail owing to extensive efforts by a large number of contributing investigators. While the basic framework built of understanding the underlying biochemical reactions and interactions of the different players is very solid, much still needs to be done to fill in the more complicated or perhaps just less explored details that are essential for an integrated comprehension of the cellular systems that lead to safekeeping of the genome. In particular, deeper insights into the organisation of oxidative DNA damage repair in the context of the living cell should be aspired. Questions include, but are certainly not limited to: where exactly does oxidative DNA damage accumulate? How are different aspects of its repair regulated in the context of the cell cycle, especially during S-phase? How do these well-defined repair pathways perform in the context chromatin? What influence does chromatin remodelling have on these reactions? How is the interplay between the various different and sometimes overlapping repair activities managed? What are there more profound tissue- and cell-type specific differences in these mechanisms that underlie the differences in disease predisposition? Unravelling these riddles will necessitate considerable efforts, but is expected to yield important insights to further clarify the connection between oxidative DNA damage, its repair and human diseases. Considering the clear involvement of oxidative DNA damage repair in the onset and pathogenesis of many different human pathologies, more detailed understanding of these mechanisms in the context of the organism might well pave the way for successful preventive and therapeutic approaches involving the repair of oxidatively damaged DNA.

Conflict of interest statement

The author declares no conflict of interest.

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